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Organometallic derivatives of quinoline and isoquinoline

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ORGANOMETALLIC DERIVATIVES OF QUINOLINE AND ISOQUINOLINE

by

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INTRODUCTION

In the field of organic synthetic chemistry the organolithium and organomagnesium reagents enjoy a wider degree of applicability than any other group of organometallic compounds. The organolithium and organomagnesium compounds are prepared and handled with relative ease in the laboratory. Another important criterion of their usefulness is that they complement each other in the sense that where a certain organomagnesium compound cannot be prepared, the corresponding organolithium compound can be made in good yield.

Of the very highly reactive types of organolithium compounds which are capable of the halogen-metal interconversion reaction, n-butyllithium has been used most extensively in this reaction[1].

By use of the halogen-metal interconversion reaction heretofore inaccessible organolithium compounds of quinoline and isoquinoline were obtained in good yields, such as 2- and 4-quinolyl- and 1- and 4-isoquinolyllithium.

Part of this work was an attempt to prepare some new 1-substituted isoquinolines and 2-substituted quinolines by the addition of some alkyl- and aryllithium reagents to the anil linkage of isoquinoline and quinoline, respectively.

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[1]R. G. Jones and H. Gilman in Adams "Organic Reactions", Vol. 6, New York, J. Wiley & Sons, Inc. 1951.

A second part of this investigation was undertaken to prepare some quinoline and isoquinoline derivatives which could be used as organic liquid scintillator solutes and to correlate the scintillator activity with the activity of closely related aza-aromatic heterocycles. The scintillator activity of these compounds was evaluated by Drs. Wright H. Langham, F. Newton Hayes and Donald G. Ott of the Los Alamos Laboratories.

A third phase of this work was to synthesize some quinoline-boronic acid derivatives for possible use in brain tumor therapy.

HISTORICAL

Introduction

The historical section is devoted to a review of the chemical literature which concerned the organometallic derivatives of quinoline for the past twenty-five years and the organometaloid derivatives of quinoline for the past fifty years. For a more thorough discussion of the earlier work and other studies related to this subject, the following literature citations should be consulted[2-6].

The numbering system for pyridine(I), quinoline (II), and isoquinoline (III) is that which is employed by Chemical Abstracts.

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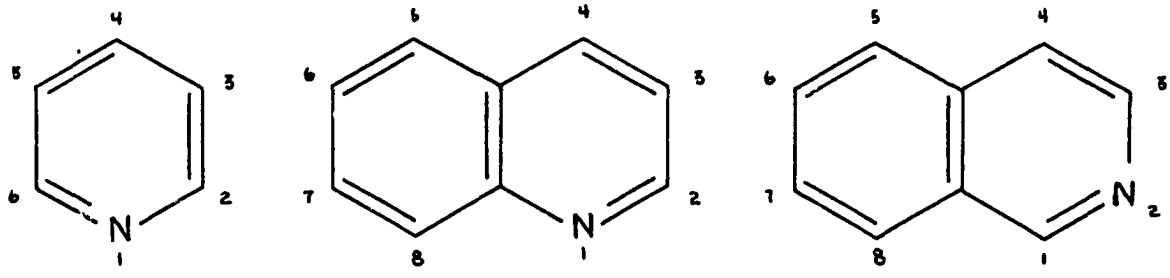
[2]S. M. Spatz, Unpublished Ph.D. Thesis. Ames, Iowa, Iowa State College Library (1941).

[3]G. C. Gainer, Unpublished Ph.D. Thesis. Ames, Iowa, Iowa State College Library (1946).

[4]J. A. Beel, Unpublished Ph.D. Thesis. Ames, Iowa, Iowa State College Library (1949).

[5]W. A. Gregory, Unpublished M.S. Thesis. Ames, Iowa, Iowa State College Library (1942).

[6]M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances", New York, Prentice-Hall, Inc. (1954).



I II III

The Addition of Grignard Reagents to Pyridine, Quinoline, and Isoquinoline

The first reported addition of a Grignard reagent to an aza-aromatic heterocycle was the result of an investigation by Oddo[7]. A small yield of 2-phenylquinoline was obtained when a mixture of magnesium, quinoline, bromobenzene, and toluene was heated on an oil bath at 140°, or when a mixture of phenylmagnesium bromide, quinoline, and pyridine was refluxed for two hours. In a later investigation Bergstrom and McAllister[8] obtained 2-phenylquinoline in a yield of 66% by autoclaving an ethereal solution of quinoline and phenylmagnesium bromide at 150-160° for three hours.

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[7] B. Oddo, Atti accad. naz. Lincei Rend., [5], 16, Part I, 413, 538 (1907).

[8] F. W. Bergstrom and S. H. McAllister, J. Am. Chem. Soc., 52, 2845 (1930).

Bergmann and Rosenthal[9] added benzylmagnesium chloride to pyridine and isolated a compound which they thought to be 2-benzylpyridine. Later work by Veer and Goldschmidt[10] demonstrated that the 2-isomer was not the product from this reaction, but 4-benzylpyridine was obtained. Bergmann and Rosenthal had been misled by the fact that both the 2- and 4-isomers formed picrates which melted at the same temperature. Veer and Goldschmidt employed Adams catalyst in dilute hydrochloric acid to reduce the 4-benzylpyridine and 2-benzylpyridine to the corresponding piperidine derivatives. 2-Benzylpyridine gave rise solely to 2-benzylpiperidine, but the 4-isomer gave both 4-benzylpiperidine and 4-hexahydrobenzylpiperidine.

Later Fuson and co-workers[11] in an attempt to replace the methoxyl group of 2-methoxyquinoline by means of benzylmagnesium chloride obtained a compound which was shown to be 2-methoxy-4-benzyl-1,4-(or 3,4-)dihydroquinoline.

More recently allylmagnesium bromide was found to react with a series of the aza-aromatic heterocycles. The reactivity

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[9]E. Bergmann and W. Rosenthal, J. prakt. chem., 135, 267 (1932).

[10]W. L. C. Veer and St. Goldschmidt, Rec. trav. chim., 65, 793 (1946).

[11]R. C. Fuson, H. L. Jackson, and E. W. Grieshaber, J. Org. Chem., 16, 1529 (1951).

of the heterocycles toward the allylmagnesium bromide was found to increase in the series: pyridine << quinoline ≅ isoquinoline < phenanthridine ≅ acridine. The position assumed by the entering allyl group was always alpha or gamma to the nitrogen atom[12]. As in the case of the reaction between benzylmagnesium chloride and pyridine which yielded 4-benzylpyridine, the only product which was isolated from the reaction of allylmagnesium bromide and pyridine was 4-allylpyridine. This fact was established by hydrogenating the compound to the corresponding 4-n-propyl- and by comparing the infrared spectrum of the picrate of this compound with the infrared spectrum of an authentic sample of 4-n-propylpyridine picrate. Both of the spectra were superimposible.

The Addition of Organolithium Reagents to Pyridine, Quinoline, Isoquinoline and Some of Their Derivatives

The first addition of an organolithium reagent to an aza-aromatic heterocycle was reported by Ziegler and Zeiser[13]. They observed that, on addition of a one normal solution of an alkyllithium compound to pyridine, heat was evolved until

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[12]H. Gilman, J. Eisch, and T. S. Soddy, J. Am. Chem. Soc., 79, 1245 (1957).

[13]K. Ziegler and H. Zeiser, Ber., 63, 1847 (1930).

one mole of the lithium compound had been added. Upon heating the reaction mixture, a powdery precipitate was deposited in the reaction flask. This precipitate was considered to be lithium hydride, because hydrogen was evolved on treatment of this solid with water. From this reaction there was isolated a 2-alkylpyridine. Further investigation by the same authors[14] showed that this reaction was also applicable to quinoline and isoquinoline. When quinoline or isoquinoline was treated with an organolithium reagent, however, the product that was isolated on hydrolysis was the 1,2-dihydro derivative of quinoline or isoquinoline. The aromaticity of the ring could be restored readily by oxidation of this 1,2-dihydro intermediate with nitrobenzene[14]. This reaction has since been employed extensively in the preparation of 2-substituted pyridine, quinoline, and isoquinoline derivatives[1,2,15].

Although the course of the addition of phenylmagnesium bromide and phenyllithium to benzophenone-anil, which contains an external azo-methine linkage, in ether was shown earlier to proceed by 1,4- and 1,2-addition, respectively,[16,17] the

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[14]K. Ziegler and H. Zeiser, Ann., 485, 174 (1931).

[15]H. Gilman, C. G. Stuckwisch, and J. F. Nobis, J. Am. Chem. Soc., 68, 326 (1946).

[16]H. Gilman, J. E. Kirby, and C. R. Kinney, J. Am. Chem. Soc., 51, 2252 (1929).

[17]H. Gilman and R. H. Kirby, J. Am. Chem. Soc., 55, 1265 (1933).

addition of both organometallic reagents to benzalquinaldine, however, formed α-benzohydrylquinaldine by 1,4-addition[18,19].

Incidental to the preparation of 2-(p-aminophenyl)quinoline from quinoline and the lithium salt of p-aminophenyllithium, Gilman and Gainer[20] isolated a secondary product which was considered to have arisen from 1,4-addition to the previously 2-substituted quinoline.

Ziegler and Zeiser[14] had reported earlier that, from a reaction of phenyllithium and quinoline, they had isolated in addition to 2-phenylquinoline a small quantity of lower melting product which they thought might be 4-phenylquinoline.

In order to learn whether 1,4-addition had actually occurred, Gilman and Gainer treated 2-phenylquinoline with phenyllithium[20]. The compound that was obtained melted at 86-87° which was not the melting point of 2,4-diphenylquinoline. A possibility that was next considered was the addition of a second molecule of phenyllithium to the azo-methine linkage of the 2-phenylquinoline to form 2,2-diphenyl-1,2-dihydroquinoline. The preparation of 2-phenyl-2-(p-tolyl)-1,2-dihydroquinoline by the addition of phenyl- and p-tolyllithium to 2-p-tolylquinoline

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[18]A. Hoffman, M. W. Farlow, and R. C. Fuson, J. Am. Chem. Soc., 55, 2000 (1933).

[19]H. Gilman and G. C. Gainer, J. Am. Chem. Soc., 71, 2327 (1949).

[20]H. Gilman and G. C. Gainer, J. Am. Chem. Soc., 69, 877 (1947).

and 2-phenylquinoline, respectively, showed that the azomethine linkage of the 2-arylquinoline was attacked by the aryllithium reagents.

In 1951, Gilman and Beel[21] extended the study of the reaction of 2-substituted quinolines with organometallic compounds. When phenyllithium was added to a solution of p-tolyl-2-quinolyl sulfide, the quinolyl sulfide was cleaved, and this resulted in yields of 57% and 47% of p-thiocresol and 2-phenylquinoline, respectively. Other 2-substituted quinolines such as 2-phenoxy-, 2-ethoxy-, and 2-alloxyquinoline were cleaved successfully.

Of the organometallic compounds employed in this cleavage study, phenyllithium gave the best yields of products, because, although it was quite reactive, the side reactions were not extensive. This fact was illustrated by the low yield of 2-n-butylquinoline that was obtained on treatment of 2-chloroquinoline with n-butyllithium at room temperature. Under identical conditions phenyllithium gave a 65% yield of 2-phenylquinoline.

The attempt to cleave the same substituted quinolines with phenylmagnesium bromide gave low yields of 2-phenylquinoline, and high recoveries of starting material which was not

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[21]H. Gilman and J. A. Beel, J. Am. Chem. Soc., 73, 774 (1951).

unexpected in view of the known lower reactivity of phenylmagnesium bromide as compared to phenyllithium. Interestingly enough 2-chloroquinoline gave a 31.2% yield of 2-phenylquinoline when treated with phenylmagnesium bromide. When 2-chloroquinoline was treated with phenylcadmium chloride, an organometallic compound of lower reactivity than phenylmagnesium bromide, no reaction occurred with 2-chloroquinoline. When 2-ethoxyquinoline was treated with n-butyllithium in ether at room temperature and then carbonated, a 7.8% yield of 2-ethoxyquinoline-3-carboxylic acid was obtained[22]. The predominant reaction, however, was the formation of 2-n-butylquinoline in 57.9% yield. This product could have resulted either from a preliminary addition of the n-butyllithium to the azo-methine linkage followed by elimination of lithium ethoxide or ethanol, or from a direct cleavage of the ethoxy grouping by the n-butyllithium.

Grignard Reagents of Pyridine and Quinoline

Initial attempts to prepare any of the organomagnesium reagents of pyridine by the classical Grignard reaction met

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[22]H. Gilman and J. A. Beel, J. Am. Chem. Soc., 73, 32 (1951).

with failure[23]. S. A. Harris[24] was one of the first investigators to find evidence for the formation of the Grignard reagent from 3-bromo- and 2-iodopyridine. He observed that on treatment of these halogenated pyridines with magnesium, the formation of the Grignard reagent took place as indicated by a positive Color Test I[25], but side reactions set in with the subsequent formation of a tarry product.

Grignard[26] in 1934 was first to suggest a modification in the classical method for the preparation of some hitherto unavailable organomagnesium reagents. This procedure which was termed the "entrainment" reaction required the addition of an "auxiliary" bromide. Grignard attributed the good results which were obtained with this method to the fact that the "auxiliary" bromide had a constant cleaning action on the magnesium surface. He suggested that the best yields were obtained when exactly one mole of ethyl bromide was added per mole of the desired bromide[27]. The possibility was also considered that the double interconversion,

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[23]F. Sachs and L. Sachs, Ber., 37, 3088 (1904).

[24]S. A. Harris, Unpublished Ph.D. Thesis. Ames, Iowa, Iowa State College Library (1931).

[25]H. Gilman and J. Schulze, J. Am. Chem. Soc., 47, 2002 (1925).

[26]V. Grignard, Compt. rend., 198, 625 (1934).

[27]V. Grignard, Compt. rend., 198, 2217 (1934).

$$RMgBr + R'Br \longrightarrow R'MgBr + RBr ,$$

might be the real mechanism of the reaction[28].

Later Overhoff and Proost[29] presented evidence which failed to support either of the above views. In their case they found that the addition of one mole equivalent of ethyl bromide was unnecessary. When added simultaneously with a bromopyridine very little difference in yield was noticed when the amount of ethyl bromide varied from 0.25 to one mole. This result would have suggested a purely mechanical cleansing action. Good yields (38%) were also obtained when one of the bromopyridines was added to one mole of ethylmagnesium bromide in the presence of magnesium metal. When this oil was treated with benzaldehyde, a small amount of the α-phenyl-2-pyridinemethanol was isolated. The yield of this carbinol was so low that Urion's mechanism for the "entrainment" reaction could not be the explanation for the good yields of product that were usually obtained with this reaction. Based on the above facts, Overhoff and Proost suggested a possible mechanism for the "entrainment" reaction which has been thoroughly discussed by Gregory[5].

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[28] E. Urion, Compt. rend., 198, 1244 (1934).

[29] J. Overhoff and W. Proost, Rec. trav. chim., 57, 179 (1938).

Although Overhoff and Proost were unable to completely elucidate the mechanism of the "entrainment" reaction, their preparation of the first Grignard reagent of pyridine in good yield was responsible for opening another synthetic route to pyridine derivatives. For example, Proost and Wibaut[30] employed this reaction to prepare some 2-pyridylcarbinols by treating some alkyl and aryl ketones with 2-pyridylmagnesium bromide.

In 1951 Gilman, Gregory, and Spatz[31] employed 2-pyridyllithium to prepare 2-pyridylmagnesium bromide by the addition of an ethereal solution of anhydrous magnesium bromide to 2-pyridyllithium at -20°.

In 1950 the Grignard reagent of 3-bromopyridine was prepared by the "entrainment" reaction[32]. Since the bromine atom was attached to the 3-position, the reactivity was expected to be less than that of the bromine atom in the 2-position. In order to compensate for this reduced reactivity, the amount of ethyl bromide, the "auxiliary" agent, added was increased to 0.3 mole per 0.1 mole of 3-bromopyridine. The 3-pyridylmagnesium bromide was added to some alkyl and aryl ketones. The

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[30]W. Proost and J. P. Wibaut, Rec. trav. chim., 59, 971 (1940).

[31]H. Gilman, W. A. Gregory, and S. M. Spatz, J. Org. Chem., 16, 1788 (1951).

[32]J. P. Wibaut, H. van der Voort, and R. Markus, Rec. trav. chim., 69, 1048 (1950).

yields of 3-pyridylcarbinols that were obtained were not impressive (17%). When the ratio of the "auxiliary" agent was increased to 0.4 mole per 0.1 mole of the 3-bromopyridine, the yields of the 3-pyridylcarbinols which were obtained were much improved (70%)[33].

Wibaut and Heeringa[34] have more recently found that 4-pyridylmagnesium chloride could be prepared by the "entrainment" reaction. The ratio of ethyl bromide, the "auxiliary" agent, to 4-chloropyridine that was employed was three to one. The best results were achieved when the coupling of the 4-pyridylmagnesium chloride with the second component was carried out in a higher boiling solvent than ether. Benzene appeared to be the most satisfactory solvent.

The attempt to prepare the Grignard reagents of quinoline and isoquinoline has not been investigated extensively. The only reported preparation of a Grignard reagent of quinoline by an "entrainment" reaction was 2-quinolylmagnesium bromide. The yield of this reagent was so small that it could not be used as a synthetic reagent[34].

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[33]J. P. Wibaut and H. G. P. van der Voort, Rec. trav. chim., 71, 798 (1952).

[34]J. P. Wibaut and L. G. Heeringa, Rec. trav. chim., 74, 1003 (1955).

Organolithium Reagents of Pyridine, Quinoline, and Isoquinoline

By the halogen-metal interconversion reaction

The first attempts to prepare organolithium compounds from 2-bromopyridine, 2-bromoquinoline, and 3-bromoquinoline by the halogen-metal interconversion reaction[1] were carried out at the temperature of refluxing ether for twenty hours[35]. No acid, subsequent to carbonation, could be isolated.

Gilman and Spatz[36] by proper selection of conditions were able to prepare 3-quinolyllithium in 52% yield by means of the halogen-metal interconversion reaction of 3-bromoquinoline with n-butyllithium at -35°. Later, these investigators were able to obtain 2-litho-4-methylquinoline by treatment of 2-iodo-4-methylquinoline with n-butyllithium at -5° for five minutes[37]. Under the conditions that were employed in this reaction, the n-butyllithium did not attack the azo-methine linkage of the 2-iodo-4-methylquinoline or metalate its methyl group. Moderately low temperatures and short reaction periods were found

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[35] I. Banner, Unpublished M.S. Thesis. Ames, Iowa, Iowa State College Library (1939).

[36] H. Gilman and S. M. Spatz, J. Am. Chem. Soc., 62, 446 (1940).

[37] H. Gilman and S. M. Spatz, J. Am. Chem. Soc., 63, 1553 (1941).

to be essential in the preparation of 3-quinolyllithium from 3-bromoquinoline and n-butyllithium in order to avoid a possible attack at the azo-methine linkage by the n-butyllithium.

The same investigators employed the halogen-metal interconversion reaction to prepare some organolithium reagents of pyridine. The bromopyridine derivatives were treated with n-butyllithium at low temperatures (-35 to 0°) and short reaction times (5 to 15 minutes). Some of the types of pyridyllithium reagents which were reported by them were as follows: 2-pyridyllithium (62%)[38a], 3-pyridyllithium[38b], and 5-bromo-3-pyridyllithium[38c] (41%) from 3,5-dibromopyridine and slightly more than two equivalents of n-butyllithium.

In 1952, Murray III and Langham[39] prepared 4-lithiopyridine from 4-bromopyridine and n-butyllithium at -40° by the halogen-metal interconversion reaction. The 4-lithiopyridine was employed in the preparation of radioactive isonicotinic acid by the action of radioactive $C^{14}O_2$. In later studies by other investigators[40,41] 2-, 3-, and 4-lithiopyridines were used

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[38](a) S. M. Spatz, Iowa State Coll. J. Sci., 17, 129 (1942); (b) S. M. Spatz and H. Gilman, Proc. Iowa Acad. Sci., 47, 262 (1940); (c) H. Gilman and S. M. Spatz, J. Org. Chem., 16, 1485 (1951).

[39]A. Murray III and W. H. Langham, J. Am. Chem. Soc., 74, 6289 (1952).

[40]L. Berger, A. Ziering, and J. Lee, J. Org. Chem., 12, 905 (1947).

[41]H. E. French and K. Sears, J. Am. Chem. Soc., 73, 469 (1951).

to achieve the syntheses of a number of new carbinols.

Very recently 2-quinolyl- and 1-isoquinolyllithium have been prepared by the halogen-metal interconversion reaction with n-butyllithium and the respective bromoquinoline derivative at -50°.[42] Each of these organolithium compounds was characterized by a reaction with benzophenone to yield the corresponding tertiary alcohols. When 2-quinolyl- and 1-isoquinolyllithium were carbonated, the predominant products were 2,2'-diquinolyl- and 1,1'-isoquinolyl ketone. Ketone formation on carbonation of organolithium derivatives has been observed earlier[43]. This reaction has been shown to involve the initial formation of the carboxylic acid salt which was attacked again by the organolithium reagent[44].

By the metalation reaction

Ziegler and Zeiser[11] found that treatment of α-picoline and quinaldine with phenyllithium gave α-picolyllithium and quinaldyllithium due to the lateral metalation of the methyl group.

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[42] H. Gilman and T. S. Soddy, J. Org. Chem., 22, 565 (1957).

[43] H. Gilman and P. D. Van Ess, J. Am. Chem. Soc., 55, 1758 (1933).

[44] H. F. Bluhm, H. V. Donn, and H. D. Zook, J. Am. Chem. Soc., 77, 4406 (1955).

In 1948, Prijs, Lutz, and Erlenmeyer[45] found that γ-picoline could be laterally metalated with phenyllithium, but under the conditions that were employed, heating on a steam plate for ten hours, the phenyllithium also attacked the azo-methine linkage. The product that was isolated ultimately was 2-phenyl-4-pyridineacetic acid in a yield of 16%.

Later studies by Zelinski and Benilda[46] and Goldberg, Barkley, and Levine[47] improved the method of preparing α-picolyllithium. When molar equivalents of α-picoline, phenyllithium, and an alkyl halide were employed, the yields of the α-alkylated pyridines were generally between 50 to 60%. When the ratio of α-picoline, phenyllithium, and alkyl halide was increased to 2:2:1, respectively, the yields of α-alkylated pyridines were found to lie between 70 to 80%[48].

By employing methyllithium as the metalating agent, Osuch and Levine[48] found that γ-picoline could be laterally metalated without the accompanying addition of the methyllithium to the azo-methine linkage. Good yields (60 to 70%) of

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[45] B. Prijs, A. H. Lutz, and H. Erlenmeyer, Helv. Chim. Acta, 31, 571 (1948).

[46] R. P. Zelinski and M. Benilda, J. Am. Chem. Soc., 73, 696 (1951).

[47] N. N. Goldberg, L. B. Barkley, and R. Levine, J. Am. Chem. Soc., 73, 4301 (1951).

[48] C. Osuch and R. Levine, J. Am. Chem. Soc., 78, 1723 (1956).

α-alkylated pyridines were obtained by utilizing α-picoline, methyllithium, and an alkyl halide in a ratio of 2:2:1, respectively.

Other Organometallic Derivatives of Quinoline and Isoquinoline

Mercury

In 1928, Ukai[49] heated isoquinoline with mercury (II) acetate at 150-160° and obtained a compound which he thought was 5- or 8-chloromercuriisoquinoline. A later investigation demonstrated that the compound was 4-chloromercuriisoquinoline[50]. This fact was established by the preparation of the monobromo derivative of the chloromercuriisoquinoline. The bromoisoquinoline was subjected to a series of degradative reactions which showed the compound to be 4-bromoisoquinoline[51]. When quinoline was treated with mercury (II) acetate, the compound which was isolated, after the addition of a chloride salt, was 3-chloromercuriquinoline.

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[49] T. Ukai, J. Pharm. Soc. Japan, 48, 374 (1928). [C. A., 23, 33166 (1929).]

[50] T. Ukai, J. Pharm. Soc. Japan, 51, 542 (1931). [C. A., 25, 5427 (1937).]

[51] T. Ukai, J. Pharm. Soc. Japan, 48, 877 (1928). [C. A., 23, 1642 (1929).]

Tin

The only tin derivative of quinoline reported was prepared in this Laboratory[52]. Triphenyl-3-quinolyltin was synthesized by the reaction of 3-quinolyllithium with triphenyltin (IV) chloride in diethyl ether at -15°.

Organometaloid Derivatives of Quinoline

Arsenic

Fränkel and Löwy[53] in 1913 prepared α-methylquinoline-arsonic acid by the condensation of arsanilic acid with acetaldehyde. This intermediate was cyclized in the presence of hydrobromic acid.

Berlingozzi[54] coupled some amino- and hydroxyquinoline derivatives with diazotized arsanilic acid to obtain azo dyes which might have some therapeutic value. For example, 4-hydroxyquinaldine was coupled with diazotized arsanlic acid to yield 3-azo-4-hydroxyquinaldine-p-phenylarsonic acid[55].

[52] J. Eisch, Unpublished Ph.D. Thesis, Ames, Iowa, Iowa State College Library (1956).

[53] S. Fränkel and P. Löwy, Ber., 46, 2546 (1913).

[54] S. Berlingozzi, Ann. Chim. applicata, 18, 13 (1928). [C. A., 23, 838 (1929).]

[55] S. Berlingozzi, Ann. Chim. applicata, 18, 333 (1928). [C. A., 22, 1976 (1928).]

In a series of investigations between 1930 and 1932, Slater[56-58] prepared a number of 6-methoxyquinoline derivatives of o- and p-aminophenylarsonic acid. The method that was employed for the synthesis of the compounds was the Bart reaction.

A typical example of the reaction is as follows: 4-p-aminoanilino-6-methoxyquinaldine was diazotized and treated with an alkaline solution of sodium arsenite in the presence of a copper catalyst to yield p-6-methoxyquinaldyl)amino-phenylarsonic acid.

Two dialkylarsine derivatives of quinoline have been reported[59]. 3-Quinolyldimethylarsine was synthesized by a reaction which involved the addition of dimethyliodoarsine to 3-quinolyllithium at -15°. Another derivative, 2-(di-n-propyl-arsinophenyl)quinoline, was prepared by the addition of p-lithiophenyldi-n-propylarsine to quinoline at 0°.

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[56]R. H. Slater, J. Chem. Soc., 1209 (1930).

[57]H. Slater, ibid., 107 (1931).

[58]H. Slater, ibid., 2104 (1932).

[59]H. Gilman and S. Avakian, J. Am. Chem. Soc., 76, 4031 (1954).

Antimony

In 1934, Barnett, Gillieson, and Kermack[60] prepared some hydroxyquinoline derivatives of stibonic acids by a modification of the Bart reaction. A diazotized solution of 6-amino-2-hydroxyquinoline was added slowly to an ice-cold sodium antimonite solution, which contained sodium carbonate as a buffer and copper sulfate as a catalyst, to give 2-hydroxy-6-quinolinestibonic acid.

Phosphorus

Kasolapoff[61] in 1956 prepared two quinoline phosphonic acid derivatives. He employed p-aminophenylphosphonic acid and p-aminobenzylphosphonic acid in the Skraup reaction to obtain 6-quinolylphosphonic acid and 6-quinolylmethylphosphonic acid, respectively.

Tellurium

Reichel and Ilberg[62] in 1943 were the first investigators to report the preparation of a tellurium derivative of

[60]M. M. Barnett, A. H. C. P. Gillieson, and W. O. Kermack, J. Chem. Soc., 433 (1934).

[61]G. M. Kasolopoff, J. Org. Chem., 21, 1046 (1956).

[62]L. Reichel and K. Ilberg, Ber., 76B, 1108 (1943).

quinoline. By treating 2-phenyl-4-quinolinecarboxylic acid with tellurium (IV) chloride in dry carbontetrachloride for two hours on a steam bath, they obtained 4- 4-carboxy-quinolyl-(2) phenyltellurium (IV) chloride.

The Preparation of Organometallic Compounds in Tetrahydrofuran

Grignard reagents

In a splendid investigation H. Normant[63] found that excellent yields of Grignard reagents could be obtained with alkenyl and aryl chlorides by employing tetrahydrofuran as a solvent. For example, by adding a trace amount of ethyl bromide as a catalyst to the reaction mixture, a 76% yield, which was based on hydrolysis of the reaction mixture, could be obtained of p-chlorophenylmagnesium chloride from p-dichlorobenzene. The excellent yields of the alkenylmagnesium chlorides that were also obtained in tetrahydrofuran have helped to enhance greatly the scope of the Grignard reagent. In ease of formation, in versatility of application, and in the excellent yields of product, the alkenylmagnesium chlorides appeared to be analogous to the alkyl and aryl Grignard

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[63]H. Normant, Compt. rend., 239, 1510 (1954).

reagents[64,65]. Braude and Evans[66], however, have observed recently that isobutenyl bromide could not be made to react with magnesium in tetrahydrofuran under the conditions that were used by Normant.

One very interesting application of tetrahydrofuran as a solvent for the preparation of arylmagnesium halides was the reaction between o-dibromobenzene and magnesium to give o-bromophenylmagnesium bromide in a yield of 20%[67].

Seyferth[68] prepared vinylmagnesium chloride in tetrahydrofuran by employing the same technique as Normant. This Grignard reagent was used to prepare some vinyltin compounds for cleavage studies.

Rosenberg, Gibbons, Jr., and Ramsden[69] also prepared vinylmagnesium chloride in tetrahydrofuran. The reaction was catalyzed by the addition of a few drops of ethyl bromide.

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[64]H. Normant, ibid., 239, 1811 (1954).

[65]H. Normant, ibid., 240, 314, 440, 631, 1111, 1435 (1955).

[66]E. A. Braude and E. A. Evans, J. Chem. Soc., 3324 (1955).

[67]H. Heaney, F. G. Mann, and I. T. Millar, J. Chem. Soc., 4692 (1956).

[68]D. Seyferth, J. Am. Chem. Soc., 79, 2133 (1957).

[69]S. D. Rosenberg, A. J. Gibbons, Jr., and H. E. Ramsden, J. Am. Chem. Soc., 79, 2137 (1957).

Organolithium reagents

The excellent yields of Grignard reagents which were obtained in tetrahydrofuran suggested the possible use of this solvent in the preparation of organolithium compounds[70]. Although the preparation of aryllithium compounds directly from aryl fluorides and lithium gave low yields in diethyl ether, phenyl- and p-tolyllithium were prepared from fluorobenzene and p-fluorotoluene in yields of 50%. The reactions were catalyzed by the addition of their respective bromo analogues.

Further investigation demonstrated that phenyllithium could be prepared from bromobenzene in a yield of 98% at -60°[71] and from chlorobenzene in a yield of 53% at 15° in tetrahydrofuran[42]. Higher reaction temperatures resulted in lower yields of phenyllithium.

The preparation of n-butyllithium in tetrahydrofuran could best be accomplished by employing n-butyl chloride instead of n-butyl bromide, since coupling of bromo derivatives was enhanced in tetrahydrofuran. An excellent illustration of this coupling reaction in tetrahydrofuran was the preparation of

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[70]H. Gilman and T. S. Soddy, J. Org. Chem., 22, 0000 (1957).

[71]H. Gilman and B. J. Gaj, J. Org. Chem., 22, 0000 (1957).

2,2'-dibromobiphenyl in a yield of 73% from o-dibromobenzene and n-butyllithium[72].

Methyl-, n-butyl-, and phenyllithium were found to be less stable in tetrahydrofuran than in diethyl ether[71]. As expected, the order of decreasing stability of the three organolithium reagents investigated was the same as the order found in diethyl ether, namely, methyl- > phenyl- > n-butyllithium. The stability results indicated that the optimum workable temperature for methyl-, phenyl-, and n-butyllithium in tetrahydrofuran were 0°, 0 to -30°, and below -35°, respectively.

Metalations in Tetrahydrofuran

In 1942, Brown and Adams[73] were able to demonstrate that the base strength of tetrahydrofuran toward borontrifluoride was greater than diethyl ether. This superior base strength of tetrahydrofuran and some of the unusual chemical reactions[71,72] which were obtained in this solvent prompted Gilman and Gorsich[74] to investigate the potentiality of this solvent as a medium for the metalation reaction.

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[72]H. Gilman and B. J. Gaj, ibid., 22, 447 (1957).

[73]H. C. Brown and R. M. Adams, J. Am. Chem. Soc., 64, 2557 (1942).

[74]H. Gilman and R. D. Gorsich, J. Org. Chem., 22, 687, (1957).

An earlier comparative metalation study of dibenzofuran with n-butyllithium in diethyl ether, di-n-butyl ether, and petroleum ether (b.p. 28-38°) gave yields of 56%, 76%, and 1%, respectively, of 4-dibenzofurancarboxylic acid after carbonation of the metalated product. In all of these cases the reaction mixtures were refluxed for 4 to 24 hours with the yields of 4-dibenzofuryllithium increasing slightly with increased refluxing periods[75,76].

Gilman and Gorsich[74] by employing tetrahydrofuran as the solvent succeeded in metalating dibenzofuran in yields (83-86%) higher and under much milder conditions than were employed previously[75,76]. The n-butyllithium which was prepared in diethyl ether was added to a tetrahydrofuran solution of dibenzofuran at -60°, and the reaction mixture was allowed to stir between 0-5° for one hour before carbonating. The yields of 4-dibenzofuryllithium were based on the amount of pure 4-dibenzofurancarboxylic acid isolated from the carbonation mixtures.

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[75]H. Gilman, F. W. Moore, and O. Baine, J. Am. Chem. Soc., 63, 2479 (1941).

[76]H. Gilman, R. A. Benkeser, and G. E. Dunn, J. Am. Chem. Soc., 72, 1689 (1950).

In a series of studies by Wittig and co-workers[77-79] the metalation of fluorobenzene with phenyllithium at 0° in diethyl ether gave products which indicated that o-fluorophenyllithium was one of the intermediates. Under the conditions that were employed, however, o-fluorophenyllithium was too reactive to be detected successfully by the formation of derivatives as such.

A recent investigation in this Laboratory[80] has shown that o-fluorophenyllithium can be obtained in a 60% yield which was based on the o-fluorobenzoic acid that was obtained on carbonation. This preparation was accomplished by treating fluorobenzene in tetrahydrofuran with n-butyllithium which was prepared in tetrahydrofuran between -50 and -60° for seven hours. When the reaction was carried out under the same conditions, with the exception that diethyl ether was employed as the solvent, no evidence for the formation of o-fluorophenyllithium could be detected.

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[77]G. Wittig, G. Pieper, and G. Fuhrmann, Ber., 73, 1193 (1940).

[78]G. Wittig and W. Merkle, Ber., 75, 1491 (1942).

[79]G. Wittig, Naturwiss., 30, 696 (1942).

[80]H. Gilman and T. S. Soddy, J. Org. Chem., 22, 0000 (1957).

EXPERIMENTAL

Introduction

All reactions which involved organometallic compounds were carried out in an atmosphere of dry nitrogen, and the solvents which were employed in these reactions were dried over sodium wire. The glassware had been dried in an oven at 110° for at least an hour prior to use.

In all cases, unless otherwise specified, the intermediate 1,2-dihydro derivatives of quinoline and isoquinoline were oxidized with nitrobenzene to restore the aromaticity of the ring.

All melting points are uncorrected. The infrared spectra were obtained through the courtesy of the Ames Laboratory, Atomic Energy Commission. The author is indebted to Mr. Robert McCord and E. Miller Layton for obtaining the infrared spectra.

Derivatives

n-Butyllithium

A 1-liter, 3-necked, round-bottomed flask was fitted with a truebor stirrer, a combination low temperature and

nitrogen inlet, and a dropping funnel. Into the flask 400 ml. of sodium dried ether was introduced. After this apparatus had been swept with dry, oxygen-free nitrogen, 15.18 g. (2.2 g. atoms) of lithium, cut into pieces of about ¼ inch, was allowed to fall directly into the reaction flask. With the stirrer started 30 drops of a solution of 137 g. (1.0 mole) of n-butyl bromide in 200 ml. of anhydrous ether was added from the dropping funnel. After an initiation period of about 1 minute, the reaction mixture was cooled by means of a Dry Ice-acetone bath between -30 and -40°. The addition of n-butyl bromide was adjusted as to require a minimum of 2 hours for addition. After the addition was completed, the reaction mixture was permitted to rise to -15° over a period of 20 to 30 minutes. The Dry Ice-acetone bath was replaced by an ice-bath, and the reaction mixture was stirred at 0 to 2° for 2 hours. The reaction mixture was filtered under an atmosphere of nitrogen by decantation through a narrow tube loosely plugged with glass wool into a graduated dropping funnel previously flushed with nitrogen. The yield of n-butyllithium by double titration was usually 85-95%.[81]

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[81] H. Gilman and A. H. Haubein, J. Am. Chem. Soc., 66, 1515 (1944).

1-(4-Biphenylyl)isoquinoline

To a stirred solution of 13.0 g. (0.10 mole) of isoquinoline in 150 ml. of ether at 0° was added dropwise a solution of 0.085 mole of 4-biphenyllithium[82] over a period of 45 minutes. At the completion of the addition the reaction mixture was red-brown, and Color Test I[25] was negative. After hydrolysis of the reaction mixture with a saturated solution of ammonium chloride, the ether layer was separated and was dried over anhydrous sodium sulfate. On evaporation of the ether the residue which remained was oxidized with nitrobenzene. After the removal of the nitrobenzene, the residue was purified by recrystallization from ethanol to give 7.0 g. (45%) of green micro crystals, m.p. 169-170°.

Anal. Calcd. for $C_{21}H_{13}N$: N, 4.98. Found: N, 4.74.

1-(2-Biphenylyl)isoquinoline. Run I

To a stirred solution of 6.5 g. (0.05 mole) of isoquinoline in 50 ml. of anhydrous ether at 4°, an ethereal solution of 0.049 mole of 2-biphenyllithium was added dropwise over a period of ½ hour. The color turned dark-reddish brown. After

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[82]H. Gilman, C. A. Zoellner, and W. Selby, J. Am. Chem. Soc., 54, 1957 (1932).

hydrolysis with a saturated solution of ammonium chloride, the ether extract was dried over sodium sulfate. The ether was distilled, and the residue oxidized with nitrobenzene at 130° for 10 minutes. The yellow residue from the oxidation could not be purified.

Run II

To a stirred solution of 6.5 g. (0.05 mole) of isoquinoline in 50 ml. of anhydrous ether at room temperature an ethereal solution of 0.049 mole of 2-biphenylyllithium was added at a rate to maintain gentle reflux. The color became white, yellow, and finally orange-brown. After 3 hours of stirring, Color Test I was negative, and a precipitate had settled to the bottom of the reaction vessel. After hydrolysis with saturated ammonium chloride solution the ether extract was dried over sodium sulfate. The ether was distilled, and the dihydro intermediate oxidized. The product was purified by recrystallization from 95% ethanol. The melting point was 220-221°, and the yield was 14%.

Anal. Calcd. for $C_{21}H_{13}N$: N, 4.98. Found: N, 4.98.

Run III. Inverse addition

To a stirred solution of 0.043 mole of 2-biphenylyllithium in 50 ml. of ether at room temperature 6.5 g. (0.05 mole) of

isoquinoline was added dropwise over a period of ½ hour. The color of the reaction mixture at the end of the addition was orange. The reaction mixture was worked up as above, but no product was obtained.

p-Bis-(2-quinolyl)benzene

To a stirred solution of 6.5 g. (0.05 mole) of quinoline in 100 ml. of ether at 5° a suspension of p-dilithiobenzene[83] in 160 ml. of an ether-Skelly B mixture was added dropwise over a period of 15 minutes. The reaction mixture became yellow in color, and a white precipitate formed. The reaction mixture was stirred for 3 hours at which time Color Test I was negative. The reaction mixture was hydrolyzed by pouring into a saturated ammonium chloride solution. The ether-Skelly B extract was dried over sodium sulfate, and the ether-Skelly B distilled. The residue was oxidized, and the purification was effected by crystallization from benzene. The pure product melted at 246-248°. The yield was 0.2 g.

Anal. Calcd. for $C_{24}H_{16}N_2$: N, 8.43. Found: N, 8.31, 8.40.

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[83] J. Goodman, Unpublished Ph.D. Thesis. Ames, Iowa, Iowa State College Library (1955).

p-Bis-(1-isoquinolyl)benzene (attempted). Run I

To a stirred solution of 6.5 g. (0.05 mole) of isoquinoline in 100 ml. of ether at 0°, a suspension of p-dilithiobenzene in 150 ml. of ether-Skelly B was added over a period of 10 minutes. The reaction mixture turned dark yellow. On completion of the addition Color Test I was negative. The reaction mixture was hydrolyzed with a saturated solution of ammonium chloride, and the ether-Skelly B extract was dried over sodium sulfate. The ether-Skelly B was distilled, and the residue which remained after oxidation was dissolved in benzene. This residue, however, yielded only a tar when attempts were made to crystallize it from several solvents.

Run II

To a stirred solution of 6.5 g. (0.05 mole) of isoquinoline in 50 ml. of ether at 0° a suspension of p-dilithiobenzene in 150 ml. of Skelly B was added dropwise over a period of 10 minutes. The reaction mixture turned yellow-brown in color, and an amorphous tan substance separated which formed a viscous mass. At the end of the addition Color Test I was still positive. By refluxing the reaction mixture overnight, the viscous mass was made to dissolve, and Color Test I was negative. The reaction mixture was hydrolyzed with a saturated solution of

ammonium chloride. The Skelly B-ether layer was separated and dried over sodium sulfate. After distillation of the Skelly B-ether and oxidation by nitrobenzene, the residue was dissolved in benzene and chromatographed on an alumina column. The eluant was benzene, and five 25-ml. fractions were collected. When concentrated the individual fractions yielded only tarry residues which could not be purified.

4,4'-Bis-(2-quinolyl)biphenyl

To a stirred suspension of 4,4'-dilithiobiphenyl[84] at room temperature a solution of 26 g. (0.2 mole) of quinoline in 100 ml. of ether was added dropwise over a period of 15 minutes. The reaction mixture became quite warm, and the color turned yellow. After the addition was complete, the reaction mixture was refluxed for 12 hours. At the end of this period Color Test I was negative, and a yellow crystalline meal had settled to the bottom of the reaction flask. The reaction mixture was hydrolyzed with a saturated solution of ammonium chloride, and the organic layer dried over sodium sulfate. After the solvent was removed by distillation, and after the intermediate dihydro derivative was oxidized, the crude

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[84] H. Gilman, W. H. Langham, and F. W. Moore, J. Am. Chem. Soc., 62, 2327 (1940).

compound was obtained in a yield of 20 g. (50%). On purification by recrystallization from pyridine, the compound was obtained as almost colorless, shiny platelets, m.p. 317-318°.

Anal. Calcd. for $C_{30}H_{20}N_2$: N, 6.86. Found: N, 6.88, 6.91.

4,4'-Bis-(1-isoquinolyl)biphenyl (attempted). Run I

Into a 1000 ml., 3-necked, round-bottomed flask was introduced 500 ml. of an ether-benzene suspension of 4,4'-dilithiobiphenyl. The suspension was cooled to 3° by means of an ice-salt bath before adding 26 g. (0.2 mole) of isoquinoline in 100 ml. of ether. The color of the reaction mixture was brown at the completion of the addition, and Color Test I was negative. After hydrolysis with a saturated solution of ammonium chloride and subsequent oxidation, the dark, tarry residue resisted all attempts to purify it.

Run II

To a stirred solution of 0.2 mole of isoquinoline at room temperature was added dropwise a suspension of 4,4'-dilithiobiphenyl in benzene-ether. When the addition was complete, a yellow meal had separated. On hydrolysis with a saturated solution of ammonium chloride, a yellow solid separated which

was insoluble in both the water and the benzene-ether phase. The excess benzene-ether was removed by distillation under reduced pressure. The crude material which remained could not be crystallized from different solvents. Purification was attempted by the preparation of the hydrochloride salt, but this salt was insoluble in water so that a good separation could not be effected.

2-(p-Terphenyl-4-yl)quinoline

To a stirred solution of 1.3 g. (0.01 mole) of quinoline in 100 ml. of ether was added a solution of p-terphenyl-4-yllithium[85] in 100 ml. of ether. Upon completion of the addition the reaction mixture was yellow, and Color Test I was negative. The mixture was worked up, and the intermediate oxidized. The product, after recrystallization from benzene, melted at 274-275°. The yield was 1.2 g. (37%).

Anal. Calcd. for $C_{27}H_{19}N$: N, 3.90. Found: N, 3.73.

1-(p-Terphenyl-4-yl)isoquinoline (attempted). Run I

Into a 250 ml., 3-necked, round-bottomed flask was introduced 1.3 g. of isoquinoline in 50 ml. of ether. To this

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[85]H. Gilman and E. A. Weipert, J. Org. Chem., 22, 446 (1957).

solution was added, over a period of 20 minutes, a suspension of p-terphenyl-4-yllithium in 70 ml. of ether. At the end of the addition a precipitate separated. The reaction mixture was subjected to a dry air oxidation. The ether was evaporated, and the residue dissolved in benzene. The benzene extract was treated with charcoal, filtered, and evaporated slowly by means of dry air. Only a skum-like residue remained which resisted other attempts at purification.

Run II

To a stirred solution of 1.3 g. (0.01 mole) of isoquinoline in 25 ml. of ether at 0° was added a suspension of p-terphenyl-4-yllithium in 80 ml. of ether. The reaction mixture turned a yellow color, and a white suspension separated. The reaction mixture was hydrolyzed and the ether extract dried over sodium sulfate. The ether was distilled, and the residue oxidized with nitrobenzene. The nitrobenzene was distilled under reduced pressure, and the residue dissolved in benzene. On concentration of the benzene solution a green solid separated. Attempts to purify this solid have up to this time failed.

1-(α-Naphthyl)isoquinoline (attempted)

To a stirred solution of 13 g. (0.1 mole) of isoquinoline in 100 ml. of ether was added an ethereal solution of 0.097

mole of α-naphthyllithium at a rate which was sufficient to maintain gentle reflux. On completion of the addition the reaction mixture was dark green, and Color Test I was negative. After hydrolysis of the reaction mixture with a 10% solution of ammonium chloride, the ether layer was separated and dried over anhydrous sodium sulfate. On evaporation of the ether the residue which remained could not be purified.

1-(β-Naphthyl)isoquinoline (attempted)

A solution of 0.09 mole of β-naphthyllithium was added dropwise to a solution of 13 g. (0.1 mole) of isoquinoline in 100 ml. of ether at 3°. On completion of the addition the color of the reaction mixture was yellow-brown, and Color Test I was negative. The reaction mixture was hydrolyzed with a 10% solution of ammonium chloride. The ether extract was separated and dried over anhydrous sodium sulfate. On evaporation of the ether the residue which remained could not be purified.

2-Propenyl-1,2-dihydroquinoline

To a stirred solution of 13.0 g. (0.1 mole) of quinoline in 50 ml. of anhydrous tetrahydrofuran at room temperature was added dropwise 0.10 mole of allylmagnesium chloride in 125 ml. of tetrahydrofuran. The reaction mixture was red-brown in

color at the end of the addition. The reaction mixture was hydrolyzed with a saturated solution of ammonium chloride, and the tetrahydrofuran extract dried over sodium sulfate. The tetrahydrofuran was distilled, and the residue which was not oxidized with nitrobenzene was distilled under reduced pressure to yield 11.05 g. of a light yellow oil, b.p. 84.5-85° (0.05 mm.), n_D^{20} 1.6063, d_{20}^{20} 1.0343.

Anal. Calcd. for $C_{13}H_{14}N$: MR_D, 57.41. Found: MR_D, 57.38.

2-Propenylquinoline

The conditions under which this reaction were run were identical to that above. After the tetrahydrofuran was distilled, the residue was oxidized with nitrobenzene. After removal of the nitrobenzene, the residue was distilled under reduced pressure to yield 9 g. of product, b.p. 89-90° (0.15 mm.), n_D^{20} 1.6170, d_{20}^{20} 1.0379. The picrate melted at 183° (lit. value 183-184°).[86]

Anal. Calcd. for $C_{12}H_{11}N$: MR_D, 56.30. Found: MR_D, 56.70.

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[86] F. Eisele, Ber., 20, 2043 (1887).

2-Propylquinoline

This reaction was also carried out under identical conditions that were employed for the preparation of 2-propenyl-1,2-dihydroquinoline. After the tetrahydrofuran was distilled, the residue was heated at 170° for 12 hours. At the end of this period the residue was distilled under reduced pressure to give 14 g. of a product, b.p. 87° (0.1 mm.), n_D^{20} 1.5870, d_{20}^{20} 1.0193. A picrate of the compound melted at 159-160° (lit. value 160-161°).[86]

The catalytic hydrogenation of 2-propenylquinoline

To a solution of 5 g. (0.029 mole) of 2-propenylquinoline in 75 ml. of absolute ethanol was added 1 g. of palladium on calcium carbonate catalyst. The gas bottle which contained this mixture was attached to the rocking hydrogenation apparatus. The pressure of hydrogen gas that was employed was 46 lb./sq. in. and the temperature was 20°. At the end of 18 hours the pressure had dropped to 42.5 lb./sq. in. The catalyst was removed from the reaction mixture by filtration, and the ethanol was evaporated. The residue was distilled to give a light green oil, b.p. 93.5-94° (1 mm.), n_D^{20} 1.5850, d_{20}^{20} 1.0256.

The picrate melted at 162-163° (lit. value 162-163°). A mixture melting point with the picrate of an authentic sample of 2-n-propylquinoline was undepressed, and the infrared spectra of the compounds were identical.

Anal. Calcd. for $C_{12}H_{13}N$: MR_D, 56.7. Found: MR_D, 56.0.

Propenylmagnesium bromide in tetrahydrofuran

Into a 3-necked round-bottomed flask, there was introduced 25 ml. of anhydrous tetrahydrofuran and 0.1 g. atom of magnesium turnings. To this rapidly stirred mixture there was added dropwise 0.1 mole of propenyl bromide in 30 ml. of tetrahydrofuran. When 10 ml. of the propenyl bromide solution had been added, the reaction commenced vigorously which caused moderate refluxing. When the initial reaction had subsided, the remainder of the propenyl bromide was added. The yield of the Grignard reagent was 76% by total alkali titration.

2-Propenylquinoline from propenylmagnesium bromide and quinoline (attempted)

To a stirred solution of 13 g. (0.1 mole) of quinoline in 50 ml. of tetrahydrofuran at 20° was added dropwise a 0.11 mole solution of propenylmagnesium bromide. Throughout the

addition little heat was generated. The color of the reaction mixture was yellow-brown at the end of the addition. The reaction mixture was hydrolyzed and the tetrahydrofuran extract was dried over sodium sulfate. After evaporation of the tetrahydrofuran, the residue was distilled under reduced pressure to yield a colorless liquid boiling at 135° (0.25 mm.). The infrared spectrum of this liquid and one of quinoline were identical. The amount of recovered starting material was 6.5 g.

Propenyllithium

Into a flask which contained 2.2 g. (0.31 g. atom) of cut lithium wire in 75 ml. of anhydrous ether was introduced 3 ml. of 1-bromopropylene. When the reaction had initiated, which was indicated by a cloudy appearance in the reaction mixture, the remainder of the 1-bromopropylene was added dropwise in 35 ml. of anhydrous ether. The addition was regulated to insure gentle reflux of the reaction mixture. The color of the reaction mixture was light yellow-brown, and the yield of product which was based on total alkali titration was 70%.

2-Propenyl-1,2-dihydroquinoline from propenyllithium and quinoline

To a stirred solution of 13 g. (0.1 mole) of quinoline in 50 ml. of anhydrous ether at 20° was added over a period of ½ hour 0.1 mole of propenyllithium in 110 ml. of ether. The color of the reaction mixture was red on completion of the addition. The reaction mixture was hydrolyzed with a saturated solution of ammonium chloride, and the ether extract dried over sodium sulfate. After the ether was removed, the residue was distilled under reduced pressure to give a yellow oil, b.p. 75° (0.01 mm.). The yield was 7.5 g.

2-Propenylquinoline

Into a one-necked flask was introduced 6 g. of 2-propenyl-1,2-dihydroquinoline and 7 ml. of nitrobenzene. The oxidation was carried out at 180° for 15 minutes. After the nitrobenzene was removed, the residue was distilled under reduced pressure to yield 3 g. of the product, b.p. 80° (0.01 mm.). The picrate melted at 183-184°. The infrared spectra of this picrate and the picrate of the compound which was obtained from allylmagnesium chloride and quinoline in tetrahydrofuran were superimposable.

The reaction of allylmagnesium bromide with lepidine in ether

To a stirred solution of 14.5 g. (0.1 mole) of lepidine in 50 ml. of ether a 0.11 mole solution of allylmagnesium bromide in ether was added slowly. On completion of the addition the color of the reaction mixture was red. After the reaction mixture was hydrolyzed with a saturated solution of ammonium chloride, the ether layer was separated and dried over anhydrous sodium sulfate. On evaporation of the ether the residue was distilled under reduced pressure to yield 13 g. (70%) of a yellow oil, b.p. 125-127° (1.5 mm.), n_D^{20} 1.6032, d_{20}^{20} 1.009.

The infrared spectrum contained an N-H band at 2.97μ. The compound might be 4-allyl-1,4-dihydrolepidine or 2-allyl-1,2-dihydrolepidine[11].

Anal. Calcd. for $C_{13}H_{14}N$: MR_D, 62.04. Found: MR_D, 62.21.

7-Chloro-4-quinolylmagnesium chloride (attempted)

To a stirred suspension of 3.1 g. of magnesium turnings in 15 ml. of ether was added a solution of 5 g. (0.025 mole) of 4,7-dichloroquinoline in 100 ml. of ether. Attempts were made to initiate the reaction with a small crystal of iodine

and a few drops of ethyl bromide, but these methods were unsuccessful. Color Test I was negative.

The preparation of activated magnesium

Into a 250 ml., 3-necked, round-bottomed flask was introduced 100 ml. of sodium dried benzene and 5 g. (0.2 g. atom) of magnesium turnings. To this suspension was added 2.5 g. of iodine. After the slow addition of 5 ml. of sodium dried ether, the suspension turned from the dark iodine color to a light yellow color. The reaction mixture was filtered to remove the catalyst which was stored under nitrogen.

The attempted preparation of 7-chloro-4-quinolylmagnesium bromide by use of activated magnesium

Into a 250 ml., 3-necked, round-bottomed flask was introduced 2.4 g. (0.1 g. atom) of magnesium and 5 g. (0.025 mole) of 4,7-dichloroquinoline. The reaction flask was warmed sufficiently to melt the 4,7-dichloroquinoline. To this suspension was added about 0.3 g. of activated magnesium catalyst. After 4 hours no reaction was noted, and the 4,7-dichloroquinoline was recovered quantitatively.

3-Quinolylmagnesium bromide in tetrahydrofuran (attempted)

Into a 500 ml., 3-necked, round-bottomed flask were introduced 20 ml. of anhydrous tetrahydrofuran and 1.2 g. (0.05 g. atom) of magnesium turnings. To this stirred suspension was added dropwise a solution of 10.2 g. (0.05 mole) of 3-bromoquinoline in 15 ml. of tetrahydrofuran. When the reaction had not started after the addition of 5 ml. of the 3-bromoquinoline solution, the reaction mixture was warmed slightly, and a crystal of iodine was added. After the addition of a few more drops of the 3-bromoquinoline solution failed to initiate the reaction, the reaction mixture was warmed while 3 drops of n-butyl bromide were added. After 1 minute the color of the reaction mixture turned red, and it began to reflux. On completion of the addition of the 3-bromoquinoline solution, the reaction mixture was dark red in color. Color Test I was negative. After hydrolysis of the reaction mixture with a saturated solution of ammonium chloride, the tetrahydrofuran layer was separated and was dried over anhydrous sodium sulfate. On evaporation of the tetrahydrofuran the residue was distilled under reduced pressure to yield 5 g. of quinoline.

6-Quinolylmagnesium bromide (attempted)

To a stirred suspension of 0.6 g. (0.025 g. atom) of magnesium in 15 ml. of tetrahydrofuran was added dropwise

a solution of 5.2 g. (0.025 mole) of 6-bromoquinoline in 35 ml. of tetrahydrofuran. When the reaction failed to initiate, different catalytic methods, such as iodine, n-butyl bromide and heat were employed, but no reaction occurred.

4-Bromoquinoline

Into a 3-necked flask were introduced 29 g. (0.2 mole) of 4-hydroxyquinoline[87] and 200 g. of phosphorous(III) bromide. The reaction mixture was refluxed for 6 hours and then hydrolyzed by pouring onto cracked ice. This mixture was made strongly basic, and the 4-bromoquinoline was extracted with ether. This extract was dried over anhydrous sodium sulfate. After removal of the ether, the 4-bromoquinoline was distilled under reduced pressure to yield 16 g. of product, b.p. 97-99° (0.5 mm.).

4-Quinolyllithium

Into a 250 ml., 3-necked, round-bottomed flask were introduced 100 ml. of anhydrous ether and 0.015 mole of n-butyllithium in 16 ml. of ether. This solution was cooled to -50°. To this solution was added 3 g. (0.015 mole) of

[87]B. Riegel, G. R. Lappin, B. H. Adelson, R. I. Jackson, C. J. Albisetti, Jr., R. M. Dodson, and R. H. Baker, J. Am. Chem. Soc., 68, 1264 (1946).

4-bromoquinoline. A yellow suspension separated from the reaction mixture. Color Test IIA[88] was negative after 10 minutes, but Color Test I was positive.

α,α-Diphenyl-4-quinolinemethanol

To the stirred solution of 4-lithioquinoline at -50°, prepared in the preceding experiment, was added dropwise 2.7 g. (0.015 mole) of benzophenone in 100 ml. of ether. After the addition of 80 ml. of ether Color Test I was negative. The color of the reaction mixture turned light yellow, and a white, curdy precipitate formed. On hydrolysis with an ice-cold saturated solution of ammonium chloride, a white solid settled between the water and ether layers. The solid was removed by filtration and dried. The yield of crude product was 80%. On recrystallization from an ethanol (1/3)-benzene (2/3) pair the melting point was 246-248° (lit. value 247-248°)[89].

4-Quinolinecarboxylic acid

Into a 3-necked, elongated flask which was equipped with a stopcock on the bottom and an attached Dry Ice-acetone bath

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[88]H. Gilman and J. Swiss, J. Am. Chem. Soc., 62, 1847 (1940).

[89]P. Remfry and H. Decker, Ber., 41, 1008 (1908).

was introduced 0.015 mole of n-butyllithium in 100 ml. of ether. This solution was cooled to -50° at which time 3 g. (0.015 mole) of 4-bromoquinoline was added. This reaction mixture was stirred for 20 minutes at -50°. The stopcock was opened, and the yellow suspension flowed jet-wise into a vigorously stirred Dry Ice-ether slurry. The carbonation mixture was worked up in the usual manner. The basic extract was acidified to a pH of 6 and concentrated from 100 to 50 ml. The pH was lowered to 1, at which time the organic acid separated in fine white crystals. The acid melted at 249.5-250° (lit. value 253-254°)[90]. The yield was 36%. No products could be isolated from the ether extract.

2-(p-Bromophenyl)quinoline

To a stirred solution of 39 g. (0.3 mole) of quinoline in 150 ml. of anhydrous ether at 0° was added dropwise a solution of p-bromophenyllithium[91] in 600 ml. of ether. The reaction mixture turned yellow in color and remained as such throughout the addition. Although the reaction mixture was stirred overnight, Color Test I[25] remained slightly positive.

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[90]H. Skraup, Ann., 201, 303 (1880).

[91]H. Melvin, Unpublished Ph.D. Thesis. Ames, Iowa, Iowa State College Library (1954).

After refluxing the reaction mixture for 1 hour, Color Test I was negative. Hydrolysis of the reaction mixture was effected by pouring it into a saturated ammonium chloride solution. The ether layer was separated and was dried over anhydrous sodium sulfate. After evaporation of the ether the crude product was dissolved in absolute ethanol. On recrystallization from absolute ethanol the pure compound (42%) was obtained as white platelets, m.p. 121-122°.

Anal. Calcd. for $C_{15}H_{10}BrN$: Br, 27.91. Found: Br, 27.71, 27.90.

2-(p-Carboxyphenyl)quinoline

Into a 3-necked, elongated flask which was equipped with a stopcock on the bottom and an attached Dry Ice-acetone bath was introduced 0.02 mole of n-butyllithium in 17 ml. of anhydrous ether. To this solution which was cooled to -45° was added, over a period of 5 minutes, a solution of 2-(p-bromophenyl)quinoline consisting of 80 ml. of ether and 20 ml. of benzene. The reaction mixture turned green in color, but the temperature remained constant. After stirring for 25 minutes Color Test IIA was negative, and Color Test I was positive. The reaction mixture was carbonated by opening the stopcock at the bottom of the reaction vessel and permitting it to flow jetwise onto a Dry Ice-ether slurry.

The basic extract was acidified, and the solid which precipitated was filtered off. The crude yield was 75%. Recrystallization of the crude product from ethanol yielded white needles, m.p. 252-253° (lit. value 248-249°)[92].

2-[p-(Trimethylsilyl)phenyl]quinoline

For comparison purposes two methods were employed in the preparation of this compound. In Method I, p-(trimethylsilyl)-phenyllithium was added to quinoline. In Method II, trimethylchlorosilane was added to 2-(p-lithiophenyl)quinoline.

Method I

To a stirred solution of 13 g. (0.1 mole) of quinoline in 100 ml. of ether was added dropwise a 0.082 mole solution of p-(trimethylsilyl)phenyllithium in ether. At the completion of the addition the color of the reaction mixture was orange. The reaction mixture was refluxed overnight, at which time Color Test I was negative. The reaction mixture was hydrolyzed by pouring it into ice-cold water. The ether layer was separated and was dried over anhydrous sodium sulfate. After evaporation of the ether layer the residue was distilled under

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[92]J. Braun and L. Brauns, Ber., 60, 1255 (1927).

reduced pressure to give 6 g. of product, b.p. 165-166° (0.005 mm.). The product crystallized in the receiver. Recrystallization from ethanol gave 42% of white platelets, m.p. 69-70°.

Anal. Calcd. for $C_{18}H_{19}NSi$: Si, 10.13. Found: Si, 10.25.

Method II

To a stirred solution of 2.16 g. (0.02 mole) of trimethylchlorosilane in 50 ml. of anhydrous ether was added dropwise a solution of 2-(p-lithiophenyl)quinoline in 100 ml. of ether and 50 ml. of benzene at -15°. The reaction mixture turned yellow in color, and salt formation was noted. At the end of the addition Color Test I was negative. The reaction mixture was hydrolyzed with a saturated solution of ammonium chloride, and the ether layer was dried over sodium sulfate. After distillation of the ether-benzene pair the residue was dissolved in 95% ethanol and diluted with water until the incipient crystallization occurred. The melting point of the purified product was 72-73°, and the yield was 57.5%. A mixture melting point with this compound and the one from Method I showed no depression.

m-Bromophenyllithium

To a stirred solution of m-dibromobenzene in 140 ml. of ether at -35° was added 0.2 mole of n-butyllithium in 135 ml. of ether at -35°. The temperature rose to -20°, after which it was again cooled to -35°. At 3, 6, 9, 12, and 15 minute intervals 50-ml. aliquots were removed and carbonated. The carbonation mixtures were worked up in the usual manner. The optimum yield of crude m-bromobenzoic acid (72%) was realized at the 15 minute interval. The melting point of the pure acid was 152-154°.

2-(m-Bromophenyl)quinoline

To a stirred solution of 6.5 g. (0.05 mole) of quinoline in 50 ml. of ether at 0° was added dropwise 0.037 mole of m-bromophenyllithium in ether at -25°. The reaction mixture was yellow in color at the end of the addition. Hydrolysis of the reaction mixture was effected by pouring it into a saturated solution of ammonium chloride. The ether extract was dried over sodium sulfate. On evaporation of the ether the residue was oxidized with nitrobenzene for 10 minutes at 140°. The nitrobenzene was distilled under reduced pressure, and the residue recrystallized from 95% ethanol. The melting point of the pure compound was 74.5-76.0°, and the yield which

was based on a 75% halogen-metal interconversion of the m-dibromobenzene was 65%.

Anal. Calcd. for $C_{15}H_{10}BrN$: Br, 27.91. Found: Br, 27.72, 27.84.

2-(m-Carboxyphenyl)quinoline

To a stirred solution of 0.01 mole of n-butyllithium in 50 ml. of ether at -30° was added 2.5 g. (0.009 mole) of 2-(m-bromophenyl)quinoline. The reaction mixture turned green in color. At the end of 20 minutes Color Test IIA was negative, but Color Test I was positive. The reaction mixture was carbonated by pouring jet-wise into a Dry Ice-ether slurry. On working up the carbonation mixture in the usual manner the basic extract yielded 1.5 g. of crude acid upon acidification. This amount was equivalent to a 70% yield. The crude acid on purification from 95% ethanol melted at 215.0-215.5°.

Anal. Calcd. for $C_{16}H_{11}NO_2$: N, 5.62. Found: N, 5.59, 5.68.

2-Picolinic acid

To a stirred solution of 0.05 mole of n-butyllithium in 44 ml. of ether at -60° was added 8 g. of 2-bromopyridine.

The color of the reaction mixture turned yellow-brown. Color Test IIA was negative, and Color Test I was positive within 5 minutes. The reaction mixture was carbonated. On working up the carbonation mixture the 2-picolinic acid was isolated as the hydrochloride salt. The decomposition point was 232-234°. No ketone was isolated from the ether extract.

6-Bromo-2-picolinic acid

To a stirred solution of 0.05 mole of n-butyllithium at -60° was added 5 g. (0.02 mole) of 2,6-dibromopyridine. Color Test IIA was negative, and Color Test I was positive after 10 minutes. The reaction mixture was carbonated by pouring jet-wise into a Dry Ice-ether slurry. The basic extract yielded 3.0 g. (75%) of 6-bromopicolinic acid, m.p. 194-195° (lit. value 192-194°)[93].

2-Pyridylphenone

To a stirred solution of 2-pyridyllithium in 230 ml. of ether at -50° was added 10.3 g. (0.1 mole) of benzonitrile in 30 ml. of ether at -50°. As the temperature rose to -40° the reaction mixture turned red in color, and a suspension

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[93] H. Gilman and S. M. Spatz, J. Org. Chem., 16, 1485 (1951).

separated. After hydrolysis of the reaction mixture with 100 ml. of 10% sulfuric acid, the acidic layer was made basic and extracted five times with 25 ml. portions of ether. The ether extracts were combined and dried over sodium sulfate. On evaporation of the ether the product was distilled under reduced pressure, b.p. 114-115° (0.01 mm.). The yield of product was 10 g. or 54%.

α,α-Diphenyl-2-pyridinemethanol

This compound was prepared by two methods for comparison purposes. In Method I, benzophenone was added to 2-pyridyllithium. In Method II, phenyllithium was added to 2-pyridylphenone.

Method I

To a stirred solution of 2-pyridyllithium at -60° was added 0.05 mole of benzophenone. The temperature of the reaction mixture rose to -40°. A solid separated as the color of the reaction mixture turned dark grey. Color Test I was negative in 2 minutes. On working up the reaction mixture the yield of the compound was 61%, and the melting point was 105-106.5°.

Method II

To a stirred solution of 4.5 g. (0.025 mole) of 2-pyridylphenone at -45° was added dropwise 0.025 mole of phenyllithium in 26 ml. of ether. After the addition was complete, the reaction mixture was hydrolyzed by pouring into a saturated solution of ammonium chloride. The ether extract was dried over sodium sulfate. After evaporation of the ether the residue solidified on standing. The melting point was 105-106°. A mixture melting point with this compound and the compound which was prepared by Method I showed no depression.

4,4'-Dipyridylketone (attempted)

To a solution of 0.05 mole of n-butyllithium in 60 ml. of ether at -65° was added 0.05 mole of 4-bromopyridine in 100 ml. of ether which had been cooled to -50°. The 4-pyridyllithium precipitated as a white solid. Color Test IIA was negative, and Color Test I was positive in 10 minutes. The reaction mixture was carbonated by pouring jet-wise into a Dry Ice-ether slurry. On working up the reaction mixture no ketone could be isolated from the organic layer.

2-Quinolineboronic acid (attempted)

To a stirred solution of 16 g. (0.075 mole) of tri-n-butyl borate at -70° was added 0.04 mole of 2-quinolyllithium at -60° dropwise over a period of 45 minutes. Color Test I was negative. On completion of the addition, the reaction mixture was hydrolyzed by pouring into an ice-cold saturated solution of ammonium chloride. The ether layer was separated and dried.

After standing for a while a second liquid began to appear throughout the water layer. This liquid was extracted with ether and the ether dried. The ether was evaporated, and the residual liquid was distilled under reduced pressure to yield a product which was shown to be quinoline in a yield of 63%.

From the original ether layer only butyl alcohol was recovered.

3-Quinolineboronic acid (attempted)

To a stirred solution of 23 g. (0.1 mole) of tri-n-butyl borate in 100 ml. of ether at -70° was added 0.025 mole of 3-quinolyllithium at -15°. The addition required 1 hour, and at its completion Color Test I was negative. The reaction mixture was hydrolyzed with a saturated solution of ammonium

chloride. The ether layer was extracted with 10% sodium hydroxide. The basic extract was acidified to give 0.5 g. of a crude product which has thus far resisted all attempts at purification.

2-Pyridineboronic acid (attempted)

To a stirred solution of 44 g. (0.2 mole) of tri-n-butyl borate in 100 ml. of ether at -70° was added 0.075 mole of 2-pyridyllithium at -45°. The addition required 1 hour. The reaction mixture was hydrolyzed by pouring into a saturated solution of ammonium chloride. The ether layer was extracted with base. Acidification of the basic extract yielded no acid.

2-(m-Boronophenyl)quinoline

To a stirred solution of 6 g. (0.025 mole) of tri-n-butyl borate in 100 ml. of ether at -60° was added dropwise over a period of 45 minutes 0.007 mole of 2-(m-lithiophenyl)quinoline in 100 ml. of ether at -40°. The reaction mixture turned yellow-brown in color. Color Test I was negative on completion of the addition. The reaction mixture was hydrolyzed by pouring it into an ice-cold saturated solution of ammonium chloride. The ether layer was extracted with three 25-ml. portions of 10% potassium hydroxide. The basic extract was

acidified. The crude acid which was obtained melted between 203-210°. The yield was 10%. On recrystallization from benzene-ethanol, the melting point was 242-244°. On the basis of the neutral equivalent, the acid was obtained in the form of its anhydride.

Anal. Calcd. for $C_{15}H_{10}BNO$: B, 4.67; neut. equiv., 231.

2-(p-Boronophenyl)quinoline (attempted)

To a stirred solution of 24 g. (0.1 mole) of tri-n-butyl borate in 200 ml. of ether at -50° was added dropwise over a period of 75 minutes 0.025 mole of 2-(p-lithiophenyl)quinoline in 100 ml. of ether at -40°. The reaction mixture turned green in color. Color Test I was negative on completion of the addition. The reaction mixture was worked up in the same manner as the above reaction, but no product was isolated.

Triphenyl-2-quinolylsilane (attempted)

To a stirred solution of 2.9 g. (0.01 mole) of triphenylchlorosilane in 100 ml. of ether at room temperature was added dropwise a solution of 0.007 mole of 2-quinolyllithium in ether. At the completion of the addition the color of the reaction mixture was dark red. Color Test I was negative. The

reaction mixture was hydrolyzed by pouring into a saturated solution of ammonium chloride. The ether extract was dried over sodium sulfate. On distillation of the ether, the residue was dissolved in Skelly B. After one recrystallization the melting point was 233-234°, and the amount was 1 g. A mixture melting point with an authentic specimen of hexaphenyldisiloxane showed no depression.

Trimethyl-2-quinolylsilane (attempted)

To a stirred solution of 2.16 g. (0.02 mole) of trimethylchlorosilane in 100 ml. of ether was added a 0.015 mole solution of 2-quinolyllithium at -50°. On completion of the addition the reaction mixture was red in color, and a precipitate had formed. The reaction mixture was hydrolyzed, and the ether extract was dried over sodium sulfate. After the ether was removed by distillation the residue was dissolved in methanol. Attempts to purify this small amount of solid were unsuccessful. The methanol was concentrated, and the small amount of oil remaining was distilled under reduced pressure. The boiling point was 54° at 0.01 mm. This liquid was shown to be quinoline by the formation of the picrate which melted at 203-204°.

2-Mesityllithium

To a stirred suspension of 0.12 g. atom of cut lithium wire in 25 ml. of tetrahydrofuran at room temperature was added dropwise 10 g. (0.05 mole) of 2-bromomesitylene in 45 ml. of tetrahydrofuran. The rate of addition was regulated to maintain gentle reflux. On completion of the addition the reaction mixture turned red-brown in color. The yield was 80% based on total alkali titration.

The metalation of 2-phenylquinoline (attempted)

To a stirred solution of 2.05 g. (0.01 mole) of 2-phenylquinoline in 100 ml. of tetrahydrofuran at -30° was added 0.01 mole of 2-mesityllithium. The color of the reaction mixture turned red, and Color Test I was weak. The reaction mixture was permitted to warm to 0° at which time it was carbonated. The basic extract when acidified yielded no acid. The tetrahydrofuran extract was concentrated to give 1.6 g. of starting material which was equivalent to 96% recovery.

2-(γ-Triphenylsilylpropyl)quinoline (attempted)

Into a 500 ml., round-bottomed flask was placed 4 g. (0.025 mole) of 2-allylquinoline, 26 g. (0.1 mole) of

triphenylsilane, and 0.32 g. of benzoyl peroxide in 30 ml. of hexane. The reaction mixture was refluxed for 14 hours. On evaporation of the hexane the viscous residue was distilled under reduced pressure. The only compound that was isolated was triphenylsilane which was recovered in 80% yield.

The reaction of allylmagnesium bromide with triphenylsilane (attempted)

To a stirred solution of 26.1 g. (0.1 mole) of triphenylsilane in 100 ml. of ether was added dropwise a solution of 0.1 mole of allylmagnesium bromide in ether at room temperature. The reaction mixture turned yellow and was stirred overnight. Color Test I was positive at the end of this period. The reaction mixture was refluxed for 2 days and was hydrolyzed with ammonium chloride solution. The ether layer was separated and dried over anhydrous sodium sulfate. On evaporation of the ether the residue was distilled under reduced pressure to yield 21 g. (80%) of triphenylsilane.

4-Chloro-2-quinolineacetic acid (attempted)

To a stirred solution of 8.5 g. (0.05 mole) of 4-chloroquinaldine in 100 ml. of ether at room temperature was added dropwise 0.045 mole of phenyllithium in 50 ml. of ether.

The color of the reaction mixture was dark red on completion of the addition. The reaction mixture was carbonated by pouring jet-wise onto a Dry Ice-ether slurry. On acidification of the basic extract no acid could be detected.

p-Lithio-p'-hydroxyazobenzene (attempted)

Into a 3-necked, round-bottomed flask was placed 0.1 mole of n-butyllithium in ether. This solution was cooled to -100° by means of an ethanol-ether-liquid nitrogen bath. To this cooled solution was added 13.8 g. (0.05 mole) of p-bromo-p'-hydroxyazobenzene in 100 ml. of ether. The temperature of the reaction mixture rose to -90°. Carbonation of the reaction mixture was effected by the addition of pulverized Dry Ice. When the Dry Ice had sublimed, the reaction mixture was hydrolyzed by pouring into ice-cold water. The ether layer was separated and dried over anhydrous sodium sulfate. On evaporation of the ether the residue which remained was crystallized from toluene to yield starting material (80%), m.p. 157-159°. The water layer was acidified, but no acid could be detected.

Bromination of quinoline (attempted)

In accordance with a procedure which was developed by

Derbyshire and Waters[94], a solution of 8 g. (0.05 mole) of silver nitrate in 50 ml. of water was added dropwise to a stirred solution of 6.5 g. (0.05 mole) of quinoline, 8 g. (0.05 mole) of bromine, 150 ml. of acetic acid, 32 ml. of nitric acid, and 25 ml. of water. A yellow precipitate of silver bromide formed immediately. The reaction mixture was hydrolyzed with a saturated solution of sodium bicarbonate. After the silver bromide was removed by filtration, the filtrate was neutralized with base. The freed base was extracted with ether. After the ether extract was dried, the ether was evaporated. The residue was distilled to yield 50% of starting material. No evidence of bromination could be found.

3-Quinolylmagnesium bromide in ether

In accordance with the "entrainment" procedure of Grignard[33], 6 g. (0.045 mole) of ethyl bromide was added to 19.2 g. (0.8 g. atom) of magnesium turnings in 100 ml. of ether. When the reaction mixture began to reflux, a solution of 40 g. (0.2 mole) of 3-bromoquinoline and 58.3 g. (0.054 mole) of ethyl bromide in 240 ml. of ether was added at a rate to maintain reflux. On completion of the addition the color was red-brown.

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[94]D. H. Derbyshire and W. A. Waters, J. Chem. Soc., 573 (1950).

3-Allylquinoline (attempted)

To the cooled 3-quinolylmagnesium bromide solution, prepared in the above reaction, was added slowly a solution of 96 g. (0.8 mole) of allyl bromide. When the addition was completed, the reaction mixture was refluxed overnight. After hydrolysis of the reaction mixture with a saturated solution of ammonium chloride, the ether layer was separated and dried over anhydrous sodium sulfate. On evaporation of the ether the residue was distilled under reduced pressure to yield a yellow liquid, b.p. 125-140° (0.1 mm.). All attempts to purify this liquid up to this time have failed.

The reaction of 4-bromoisoquinoline with magnesium in ether (attempted)

The reaction was carried out as described previously for the preparation of 3-quinolylmagnesium bromide. For the purpose of determining the approximate yield of 4-isoquinolylmagnesium bromide, the reaction mixture was carbonated, but no acid could be isolated.

DISCUSSION

The Addition of Organolithium Reagents to Quinoline and Isoquinoline

In an earlier investigation by Gainer[3], a number of 2-arylquinolines was prepared by the addition of the aryllithium reagent to quinoline. Two of these derivatives, 2-(4-biphenylyl)- and 2-(2-biphenylyl)quinoline, were isomers of the 1-(4-biphenylyl)- and 1-(2-biphenylyl)isoquinoline, respectively, which were synthesized in this study. The syntheses of 1-(4-biphenylyl)- and 1-(2-biphenylyl)isoquinoline were accomplished by the addition of 4- and 2-biphenyllithium to the anil linkage of isoquinoline. The intermediate 2-(4-biphenylyl)- and 2-(2-biphenylyl)-1,2-dihydroisoquinolines, which were formed, were oxidized with nitrobenzene to restore the aromaticity of the isoquinoline ring.

The optimum temperature for the preparation of 1-(4-biphenylyl)isoquinoline was the addition of the 4-biphenyllithium to isoquinoline at 0°. On oxidation of the 1,2-dihydro intermediate, the yield of the desired compound was 45%. Gainer[3] found that 2-(4-biphenylyl)quinoline did not require treatment with nitrobenzene to oxidize the 2-(4-biphenylyl)-1,2-dihydroquinoline intermediate to the quinoline derivative. Autooxidation was apparently sufficient to restore the aromatic

character of the quinoline ring. The yield of 2-(4-biphenylyl)-quinoline was 86% which was much higher than the isoquinoline analogue. The lower yield of 1-(4-biphenylyl)isoquinoline might have been due to the greater difficulty in purification of this compound on account of the nitrobenzene oxidation.

When an attempt was made to prepare 1-(2-biphenylyl)-isoquinoline at 0° from 2-biphenyllithium and isoquinoline, the crude material which was isolated could not be purified. This reaction was rerun at room temperature, and a 14% yield of 1-(2-biphenylyl)isoquinoline was obtained. Gainer[3] was able to prepare 2-(2-biphenylyl)quinoline in a yield of 45% under the same conditions. In the case of 2-(2-biphenylyl)-quinoline and 1-(2-biphenylyl)isoquinoline, nitrobenzene oxidation was required to aromatize their 1,2-dihydro intermediates. The higher yield of the 2-(2-biphenylyl)quinoline (45%) as compared to the 1-(2-biphenylyl)isoquinoline (14%) may have been due to a more clean-cut nitrobenzene oxidation.

When an attempt was made to prepare 1-(4-biphenylyl)- and 1-(2-biphenylyl)isoquinoline by the addition of isoquinoline to 4-biphenylyl- and 2-biphenyllithium, respectively, the yield of 1-(4-biphenylyl)isoquinoline was only 13%, and 1-(2-biphenylyl)isoquinoline could not be isolated. This result would indicate that the preferred method of preparation for 1-arylisoquinolines is the addition of the aryllithium reagent to isoquinoline.

Although many 2-arylsubstituted quinolines and 1-aryl-substituted isoquinolines have been prepared by the reaction which involved the addition of aryllithium reagents to quinoline and isoquinoline, no compounds have been reported which resulted from the treatment of quinoline or isoquinoline with an aryllithium compound which contained 2 lithium atoms. In an attempt to learn whether such a diquinolylsubstituted aryl compound could be made, two equivalents of quinoline were treated with 4,4'-dilithiobiphenyl at 0°. The compound which was obtained from this reaction was the desired 4,4'-bis-(2-quinolyl)biphenyl in a yield of 50%. A nitrobenzene oxidation was found to be unnecessary.

From the treatment of two equivalents of quinoline with p-dilithiobenzene at 0°, p-bis-(2-quinolyl)benzene was obtained in a yield of 3%. This small yield was very probably due to the failure to effect the complete halogen-metal interconversion of p-dibromobenzene with n-butyllithium. Evidence to support this contention was obtained by the isolation of a small amount of 2-(p-bromophenyl)quinoline along with the p-bis-(2-quinolyl)benzene.

When an attempt was made to prepare the analogous 4,4'-bis-(1-isoquinolyl)biphenyl and p-bis-(1-isoquinolyl)benzene by the above reaction, the desired compounds could not be obtained because the crude products which resulted from the nitrobenzene oxidation could not be purified satisfactorily.

The Addition of Aryllithium Reagents to 1-Arylisoquinoline Derivatives

Earlier workers were able to demonstrate that the addition of an aryllithium reagent to a 2-arylquinoline derivative gave a compound which could only have resulted from the aryllithium compound adding to the anil linkage[20]. At that time an attempt also was made to prepare 1-phenyl-1-(p-tolyl)-1,2-dihydroisoquinoline by treating 1-p-tolyl- and 1-phenylisoquinoline with phenyl- and p-tolyllithium, respectively, but no products could be isolated. By repeating this series of reactions and by using fractional crystallization from absolute ethanol as the purification procedure, rather than the more drastic method of distillation under reduced pressure, the 1-phenyl-(1-p-tolyl)-1,2-dihydroisoquinoline was successfully isolated in small yield[95].

The Addition of Grignard Reagents to Quinoline

In an earlier work by Gilman, Eisch, and Soddy[12], the preparation of 2-allylquinoline from the treatment of quinoline with allylmagnesium bromide in diethyl ether was achieved under

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[95]H. Gilman and T. S. Soddy, J. Org. Chem., 22, 0000 (1957).

rather mild conditions. When this reaction was repeated with the allylmagnesium chloride prepared in tetrahydrofuran and added to quinoline in tetrahydrofuran, the expected product, 2-allylquinoline, was not obtained, but a good yield (72%) of 2-propenylquinoline was isolated. This product was reduced by catalytic hydrogenation to 2-propylquinoline which was a known compound[86].

2-Propenylquinoline was made also by an unambiguous synthesis which consisted in the addition of 1-propenyllithium to quinoline. The infrared spectrum of the picrate of this product, and the spectrum of the picrate of the compound, which was obtained from the addition of allylmagnesium bromide to quinoline in tetrahydrofuran, were found to be superimposable. When the 1,2-dihydro intermediate, which was formed initially in the reaction between quinoline and allylmagnesium chloride in tetrahydrofuran, was heated to 170° for 12 hours, the compound that was isolated was shown to be 2-propylquinoline by comparison with an authentic sample. This sample was prepared by the reaction of n-propyllithium with quinoline. The absence of a terminal vinyl bond in the infrared spectrum of the 1,2-dihydro intermediate, which was isolated from the reaction of quinoline and allylmagnesium bromide in tetrahydrofuran, indicated that the compound was 2-propenyl-1,2-dihydroquinoline rather than the 2-allyl-1,2-dihydroquinoline.

The attempt to prepare 2-propenylquinoline by treating quinoline in tetrahydrofuran with 1-propenylmagnesium bromide in tetrahydrofuran has up to this time been unsuccessful. This result points to the allylmagnesium bromide, rather than the 2-propenylmagnesium bromide, as the species which attacks quinoline to give rise ultimately to 2-propenylquinoline.

A possible pathway for the formation of both the 2-propylquinoline from the 1,2-dihydro intermediate on heating, and the 1-propenylquinoline from allylmagnesium chloride and quinoline might be the isomerization of the double bond on acid catalysis while working up the reaction mixture[96]. A more thorough investigation will have to be undertaken, however, before the mechanism of formation of 2-propenylquinoline from allylmagnesium bromide and quinoline can be elucidated fully.

The Preparation of Organolithium Reagents of Pyridine, Quinoline and Isoquinoline

The organolithium compounds of pyridine, quinoline, and isoquinoline which were synthesized in this study were prepared by means of the halogen-metal interconversion reaction[1]. This

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[96]G. S. Hammond, Ames, Iowa. Information on acid catalyzed reactions. Private communication. 1957.

reaction was carried out by treating the bromo derivatives of these aza-aromatic heterocycles with n-butyllithium between -50 and -60°. Completeness of the halogen-metal interconversion reaction was determined by means of Color Test IIA. The halogen-metal interconversion reaction was usually complete within 20 minutes.

Although Gilman and Spatz[36] found -35° to be satisfactory for the preparation of 3-quinolyllithium from 3-bromoquinoline and n-butyllithium, a range of -50 to -60° was employed in the preparation of the 2- and 4-quinolyllithium, and 1-isoquinolyllithium from their respective bromo derivatives because of the greater susceptibility of the 2- and 4- positions in quinoline and the 1- position in isoquinoline to nucleophilic displacement by n-butyllithium. By the use of this method, the temperature within the reaction vessel varied less than 3 or 4° during the entire course of the halogen-metal interconversion reaction. The 2-quinolyl- and 1-isoquinolyllithium were found to be soluble in ether at this low temperature, but the 4-lithioquinoline formed a yellow suspension.

The attempt to determine the approximate yields of the 2-quinolyl- and 1-isoquinolyllithium by means of the carbonation procedure was unsuccessful since the predominant products that were isolated were 2,2'-diquinolyl- and 1,1'-diisoquinolyl ketone. A reaction that was found to be quite satisfactory for determination of the degree of the halogen-metal interconversion

reaction was the treatment of 2-quinolyl- and 1-isoquinolyllithium with benzophenone to give the respective tertiary alcohols. The yields were 70% and 68%, respectively.

The possibility that 4-quinolyllithium might form 4,4'-diquinolyl ketone on carbonation was considered, because of the vinylogous relationship which exists between 2- and 4-quinolyllithium. In order to prevent possible ketone formation, the approximate yield of 4-quinolyllithium was determined by the formation of the benzophenone adduct. The yield of 4-quinolyllithium which was based on the α,α-diphenyl-4-quinolinemethanol was 80%. When 4-quinolyllithium was carbonated under approximately the same conditions as 2-quinolyllithium, the only product which could be isolated and identified was 4-quinolinecarboxylic acid in a yield of 39%. Two possible explanations for the failure of this organolithium compound to form detectable amounts of ketone might be as follows: the lesser degree of reactivity of the 4-quinolyllithium as compared to the 2-isomer, or the 4-quinolyllithium's effective reactivity was reduced due to its insolubility in ether at -50°.

2-Pyridyllithium was prepared and carbonated under the conditions which were employed for 2-quinolyllithium to determine whether the formation of 2,2'-dipyridyl ketone could be detected. The only product which could be identified was 2-pyridinecarboxylic acid. 2-Pyridyllithium was also employed

to prepare 2-pyridyl phenyl ketone (54%) from benzonitrile at -50°. Gilman, Gregory, and Spatz[31] prepared 2-pyridyl phenyl ketone from the same reagents at -20°. The yield was 43%. The better yield of ketone at the lower temperature may have been due to a reduction in the number of secondary reactions.

Tha carbonyl grouping and the anil linkage of 2-pyridyl phenyl ketone were the only two places which were susceptible to attack by an organolithium reagent. The preferred site of attack was found to be the carbonyl grouping, for the only product which could be isolated on treatment of 2-pyridyl phenyl ketone with phenyllithium was α,α-diphenylpyridinemethanol.

An attempt to prepare 2,6-dilithiopyridine from 2,6-dibromopyridine and two equivalents of n-butyllithium by the halogen-metal interconversion reaction at -50° was unsuccessful. Evidence for the occurrence of a monohalogen-metal interconversion was obtained, however, by the isolation of 6-bromo-2-pyridinecarboxylic acid upon carbonation of the reaction mixture. The yield of this acid was 75% which was much better than that obtained at -30°. At this higher temperature earlier investigators were able to isolate only 45% of the acid[93]. The improved yield of acid at the lower temperature of -50° may have been due to a reduction in the amount of side reactions which might occur during the halogen-metal interconversion reaction such as possible

cleavage of the carbon-bromine bond by n-butyllithium to give 6-bromo-2-n-butylpyridine.

Summers[97] attempted to prepare 7-(p-lithiophenyl)quinoline by treating 7-(p-bromophenyl)quinoline with n-butyllithium at -50°, but he was able to isolate only starting material from the reaction. Because of the successful preparation of 2-quinolyllithium from 2-bromoquinoline, the vinylogous 2-(p-bromophenyl)quinoline was considered as a possible route to the lithium derivatives of X-(p-bromophenyl)quinolines. The halogen-metal interconversion reaction was employed to prepare the 2-(p-lithiophenyl)quinoline. When 2-(p-bromophenyl)quinoline was treated with n-butyllithium at -20° for 20 minutes and carbonated, the yield of 2-(p-lithiophenyl)quinoline which was based on the crude acid that was isolated was 75%. The same reaction with 2-(m-bromophenyl)quinoline resulted in a 70% yield of 2-(m-lithiophenyl)quinoline which was based on the crude 2-(m-carboxyphenyl)quinoline. The crude 2-(p-carboxyphenyl)quinoline was purer than the meta isomer. This fact may have been due to a more clean-cut reaction between the 2-(p-bromophenyl)quinoline and n-butyllithium than between the meta isomer and n-butyllithium.

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[97] R. M. Summers, Unpublished Ph.D. Thesis, Bloomington, Ind., Indiana University Library (1954). [C. A., 50, 1012 (1956).]

The Preparation of Organomagnesium Derivatives of Quinoline

Of the known chloroquinoline compounds, the 2- or 4-chloroquinolines, because of their higher degree of reactivity, appeared to offer a possible route to the preparation of a Grignard reagent of quinoline. The 4-chloroquinoline derivative which was employed for this purpose was 4,7-dichloroquinoline. All attempts to make the 7-chloro-4-quinolylmagnesium chloride proved to be unsuccessful. Catalysts such as iodine, a few drops of an alkyl bromide, or activated magnesium, were unable to initiate the reaction. A more recent report by Wibaut and co-workers[34] mentioned that 2-quinolylmagnesium bromide was obtainable from 2-bromoquinoline and magnesium in diethyl ether when the "entrainment" method of Grignard was utilized. The yield of 2-quinolylmagnesium bromide was so small, however, that this method could not be used for synthetic purposes.

The poor results which were obtained when diethyl ether was employed as a solvent for the preparation of the Grignard reagents of quinoline prompted the search for a more suitable solvent. Tetrahydrofuran was shown by Normant's work to be an excellent solvent for the preparation of some Grignard reagents which could only be prepared with great difficulty and in low yield in diethyl ether. This fact indicated that

tetrahydrofuran might possess desirable characteristics as a solvent for the preparation of Grignard reagents of quinoline.

The two bromoquinoline derivatives which were chosen to be used in tetrahydrofuran were 3- and 6-bromoquinoline. The reaction between 6-bromoquinoline and magnesium could not be initiated in tetrahydrofuran. Even the usual catalytic methods, such as iodine, a few drops of an alkyl bromide, or a combination of both of them, failed to start the reaction. 3-Bromoquinoline and magnesium reacted vigorously when the reaction mixture was heated, but on working up the reaction mixture the only product which could be isolated was quinoline (50%). A possible explanation for the loss of the bromine atom in this reaction was not attempted due to the lack of sufficient evidence. A similar result has been observed, however, by Gilman and Dietrich[98] in their attempted preparation of N-lithio-2-lithiophenothiazine from N-lithio-2-chlorophenothiazine in tetrahydrofuran. The only compound which was isolated from this reaction was phenothiazine.

Liquid Solution Scintillators

A liquid scintillator is an organic solution which interacts with a quantum of ionizing radiation to give a spectrum

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[98] H. Gilman and J. J. Dietrich, J. Org. Chem., 22, 0000 (1957).

of photons whose integrated energy is dependent on the composition of the solution and whose shape is characteristic of the solute. This system is normally used in optical combination with a photomultiplier to form a detector device which translates the movement of an ionizing particle in the scintillator into an interpretable electronic pulse.

The three components of a liquid scintillator system are usually solvent, primary solute, and secondary solute. The most effective solvents are all alkylbenzenes. The solvent most commonly employed is toluene[99]. The best primary and secondary solutes are organic molecules composed of simple aromatic rings linked in a linear manner which allows continuous conjugation. p-Terphenyl and 2,5-diphenyloxazole, which are used at about 4 g./l., are the most popular primary solutes[100].

Since good scintillating activity was obtained with three 2-pyridyl-5-phenyloxazole isomers, an attempt was made to prepare a series of polyaryls involving the quinoline and isoquinoline nucleus which are aza-aromatic heterocycles closely related to pyridine. Because the ∝-substituted derivatives of pyridine appeared to be the more promising as liquid

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[99]F. N. Hayes, B. S. Rogers, and P. C. Sonders, Nucleonics, 13, (No. 1), 46 (1955).

[100]F. N. Hayes, D. G. Ott, V. N. Kerr, and B. S. Rogers, Nucleonics, 13, (No. 12), 38 (1955).

scintillator solutes, the analogous polyaryls which contained 2-quinolyl and 1-isoquinolyl moieties were synthesized. Table 1 lists these compounds and some others of related interest. The values are measured at a concentration of 3 g./l. in toluene and are relative to 2,5-diphenyloxazole which is assigned the arbitrary value of 1.00.

The compounds without functional groups in Table 1 seem to indicate that the aza-aromatic heterocycles are inferior to other nitrogen heterocycles such as polyaryl pyrrole and oxazole derivatives. As evidence of this fact 2-(4-biphenylyl)-pyridine and 1-(4-biphenylyl)isoquinoline fail to give a significant response, even though these two compounds are closely related to p-terphenyl. Even the small response which is given by 2-(p-terphenyl-4-yl)quinoline is due probably more to the p-terphenyl moiety than to the presence of the quinoline nucleus.

In Table 1 are listed some dialkylamino derivatives of quinoline which have rather high scintillator activity. This fact seems to confirm the important influence of the dialkylamino group in increasing the scintillating ability of a solute. Arnold[101] was the first to note this effect while observing the high values which were obtained for

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[101]J. R. Arnold, Science, 127, 1139 (1955).

Table 1. Evaluation of selected compounds as liquid solution scintillators

Compound[a]	Relative Pulse Height
2-Phenylpyridine	<0.10
2-(4-Biphenylyl)pyridine	0.12
2-Phenylquinoline	<0.10
6-Chloro-2-(p-dimethylaminophenyl)-quinoline	0.63
2-(p-Diethylaminophenyl)quinoline	0.50
2-(p-Diethylaminophenyl)-6-methoxy-quinoline	0.59
2-(p-Terphenyl-4-yl)quinoline[b]	0.12
1-Phenylisoquinoline	<0.10
1-(2-Biphenylyl)isoquinoline[b]	<0.10
1-(4-Biphenylyl)isoquinoline[b]	<0.10

[a]From Dr. Henry Gilman's Research Group, Iowa State College.

[b]This thesis.

7-diethylamino-4-methylcoumarin and 2-(p-dimethylaminophenyl)-benzothiazole (0.93 and 0.90, respectively).

Another observation was made during the testing of dialkylamino derivatives of quinoline. 6-Chloro-2-(p-

dimethylaminophenyl)quinoline gave a slightly higher value (0.63) than the corresponding 2-(p-diethylaminophenyl)-6-methoxyquinoline (0.59). The value of the 2-(p-diethylaminophenyl)-6-methoxyquinoline was higher than the 2-(p-diethylaminophenyl)quinoline (0.50). The difference in value between 6-chloro-2-(p-dimethylaminophenyl)quinoline (0.63) and 2-(p-diethylaminophenyl)-6-methoxyquinoline (0.59) was again favorable to the dimethylamino group in view of previous values, which showed a consistent superiority of the methoxy derivatives over the corresponding chloro derivatives of oxazole and oxadiazole.

Boronic Acid Derivatives of Quinoline

In recent years neutron-capture therapy has been developed for the treatment of brain tumors. This therapy is an experimental procedure for achieving selective irradiation of a diseased tissue by inducing radioactivity throughout that tissue[102].

The radioactivity is induced *in situ* by the capture of thermal neutrons by a suitable target element. The energy of a thermal neutron is very low, about 0.025 electron volt.

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[102] L. C. Farr, J. S. Robertson, and E. E. Stickley, *Proc. Nat. Acad. Sci.*, 40, 1087 (1954).

When such a neutron is captured by the target element, however, millions of electron volts of nuclear energy are released by the heavy particles resulting from the breakup of the unstable intermediate nucleus[103]. The advantages of heavy particles are that they have short ranges in tissue and that they have high relative biological effectiveness. A high thermal-neutron capture cross-section is another essential requirement in selection of the target element. The element which has been employed as the target element in recent investigations and fits most closely the requirements that are mentioned above is boron 10. This element has the highest thermal-neutron capture cross-section of all the elements which decay by heavy particle emission. The heavy particles, alpha particles, which result from the boron 10 reaction ($B^{10} + n^1 \longrightarrow Li^7 + \alpha^4$) have enough energy to penetrate the tissue to a depth of only 9 microns[104].

The attempts to prepare some quinolineboronic acid derivatives met with little success. Only one acid derivative, 2-(m-boronophenyl)quinoline, could be isolated and purified in an amount sufficient for identification purposes. The yield was only 10%.

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[103]E. E. Stickley, Am. J. Roentgenol. Radium Therapy Nuclear Med., 75, 609 (1956).

[104]L. E. Farr, W. H. Sweet, J. S. Robertson, C. G. Faster, H. B. Locksley, D. L. Sutherland, M. L. Mendelsohn, and E. E. Stickley, ibid., 71, 279 (1954).

On the addition of 2-quinolyllithium to tri-n-butyl borate, Color Test I was negative which indicated that a reaction had occurred, but after the reaction mixture was worked up, only quinoline could be isolated. If the 2-quinolineboronic acid were initially formed in the reaction a possible explanation for the failure to isolate the compound might be due to the hydrolysis of the carbon-boron bond in the slightly acidic water solution. This particular bond may be quite weak due to the presence of the adjacent partially positive charges on the carbon atom of the azo-methine linkage and on the boron atom.

Although a small amount of material could be isolated from the reaction between 3-quinolyllithium or 2-(p-lithiophenyl)quinoline and tri-n-butyl borate, the crude acids could not be purified.

Miscellaneous Reactions

In a previous investigation in this Laboratory some attempts were made to prepare 2-triphenylsilylquinoline[105]. The method that was utilized for this purpose was the reaction of quinoline with triphenylsilylpotassium. This compound,

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[105]J. B. Honeycutt, Unpublished M.S. Thesis. Ames, Iowa, Iowa State College Library (1951).

however, could not be prepared by this method. With the availability of 2-quinolyllithium, the possibility was considered that 2-triphenylsilylquinoline might be prepared by the addition of 2-quinolyllithium to triphenylchlorosilane. This reaction also failed to yield the desired 2-triphenylsilylquinoline. A similar reaction between 2-quinolyllithium and trimethylchlorosilane was unsuccessful.

The recent successful use of tetrahydrofuran as a solvent for the metalation reaction suggested that this solvent might be employed as a medium for the metalation of some 2-arylsubstituted quinolines. The quinoline derivative which was chosen for the initial experiments was 2-phenylquinoline. 2-Mesityllithium was employed as the metalating agent because earlier work had shown that this organolithium reagent was too sterically hindered to attack the azo-methine linkage of 2-arylsubstituted quinolines[106]. The mesityllithium which was prepared with relative ease in tetrahydrofuran was added to the 2-phenylquinoline in tetrahydrofuran. No reaction was observed to occur. On working up the reaction mixture, only 2-phenylquinoline in 96% yield was isolated.

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[106]H. Gilman and T. L. Reid, Ames, Iowa. The action of some aryllithium compounds on some 2-substituted quinoline derivatives. Results of an investigation in the Laboratory of Iowa State College. (Typed copy). Ames, Iowa. circa 1951.

Suggestions for Further Research

An attempt might be made to extend the applicability of the halogen-metal interconversion reaction to the preparation of other organolithium reagents of quinoline and isoquinoline. Some bromoquinoline and isoquinoline derivatives which might be employed for this purpose are as follows: 3-bromoisoquinoline, 1-(p-bromophenyl)- and 1-(m-bromophenyl)isoquinoline, 2- and 4-(p-bromostyryl)quinoline, 2- and 4-(m-bromostyryl)quinoline, 4-(p-bromophenyl)- and 4-(m-bromophenyl)quinoline.

A worthwhile study would be an attempt to apply the halogen-metal interconversion reaction to the preparation of organolithium reagents of quinoline and isoquinoline from benzenoid substituted bromoquinoline and isoquinoline compounds.

A study might be undertaken to determine whether some dibromo derivatives such as 2,4-dibromoquinoline and 1,4-dibromoisoquinoline might undergo the halogen-metal interconversion reaction.

By employing Color Test I to determine the completeness of the reaction, some qualitative rate studies might be made on 1-isoquinolyl- and 2-quinolyllithium to compare their degree of reactivity.

Although 2,6-dibromopyridine would undergo a monohalogen-metal interconversion reaction to yield 6-bromo-2-pyridyl-

lithium, the dihalogen-metal interconversion reaction of this compound could not be effected. An interesting study might be undertaken to learn whether 6-bromo-2-substituted pyridines which have substituents in the 2-position other than bromine would enter into the halogen-metal interconversion reaction to yield 2-substituted-6-pyridyllithium reagents.

The unusual reaction between allylmagnesium chloride and quinoline in tetrahydrofuran as a solvent which yielded 2-propenylquinoline might be investigated further in an attempt to elucidate the mechanism of the rearrangement reaction.

The preferential attack of organolithium reagents at the site of the carbonyl grouping instead of the azo-methine linkage in such a compound as 2-pyridylphenone might be utilized to prepare some 2-pyridyl tertiary carbinols as liquid scintillator solutes. Organolithium reagents which might be used for this purpose are 2- and 4-biphenyllithium and p-terphenyl-4-yllithium.

If the organolithium reagents of pyridine, quinoline, and isoquinoline which are listed above can be prepared, they could be used in an attempt to synthesize some boronic acid derivatives for possible brain tumor therapy.

SUMMARY

A general review has been made on the preparation of organolithium and organomagnesium compounds of pyridine, quinoline, and isoquinoline as well as on the addition of organolithium and organomagnesium compounds to 2-substituted quinolines. A survey was made also of the organometallic and organometaloid derivatives of quinoline and isoquinoline.

New hitherto unavailable organolithium compounds of quinoline and isoquinoline were prepared by means of the halogen-metal interconversion reaction. 2- and 4-Bromoquinoline and 1- and 4-bromoisoquinoline were treated under mild conditions (-50 to -60°, 20 minutes) with n-butyllithium to yield the respective organolithium derivatives in good yields.

The first successful preparation of lithiophenyl derivatives of quinoline was achieved. 2-(p-Bromophenyl)- and 2-(m-bromophenyl)quinoline were treated with n-butyllithium (-20°, 20 minutes) to yield 2-(p-lithiophenyl)- and 2-(m-lithiophenyl)-quinoline, respectively.

On carbonation of 2-quinolyl- and 1-isoquinolyllithium in ether, the predominant products were found to be 2,2'-diquinolyl- and 1,1'-diisoquinolyl ketone, respectively, rather than the expected acids.

An unusual reaction was found to occur between allylmagnesium bromide and quinoline when tetrahydrofuran was employed

as the solvent. Instead of isolating 2-allylquinoline, a good yield (50%) of 2-propenylquinoline was obtained.

The addition to quinoline and isoquinoline of some polyaryl lithium reagents was described. These compounds were tested as possible liquid scintillator solutes, but their scintillator activity was found to be negligible.

Although several attempts were made to prepare some boronic acid derivatives of quinoline, 2-(m-borylphenyl)quinoline was the only compound of this type which could be isolated.

The preparation of 2-trimethylsilyl- and 2-triphenylsilylquinoline from trimethyl- and triphenylchlorosilane, respectively, and 2-quinolyllithium was unsuccessful.

A few exploratory experiments were carried out in which tetrahydrofuran was employed as a solvent for the metalation of 2-arylsubstituted quinolines. Although tetrahydrofuran was employed successfully as a solvent for other reactions in this investigation, only negative results were obtained in this case.

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